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ABSTRACT

Title of Dissertation: Behavioral consequences of kainic acid lesions and fetal transplants of the striatum.

A. Wallace Deckel, Doctor of Philosophy, 1984

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Two experiments were conducted to examine the role that the striatum has in regulating behavior. The first experiment assessed the behavioral effects caused by kainic acid lesions of the striatum in male Wistar rats 2 weeks after surgery. Specifically, kainic acid or sham lesions were made bilaterally in the dorsal striatum, and the effects of these lesions on the weight of the animals, on their spontaneous and amphetamine affected locomotor behavior, on their response to the convulsant metrazol, and on a T-maze, were measured over 2 weeks following surgery. The lesioned group showed deficits on all the behavioral measures in a pattern consistent with that reported by previous authors.

The second experiment evaluated the effect of fetal striatal transplants on behavioral deficits resulting from kainic acid striatal lesions. Three groups of female rats, including controls (sham lesion/sham transplant), lesioned only (lesioned/sham transplant), and transplanted (lesioned/day 18 fetal striatal transplant) were assessed

on seven measures, done at weekly, monthly, or 3 month intervals. Weekly measures included brief examinations of sensorimotor functioning of the rats, as well as weekly weight measures. Monthly assessments were done on locomotor behavior by examining spontaneous and amphetamine affected behavior in an open field. Finally, at 3-4 months post lesion, three behavioral measures were done, including response to the convulsant metrazol, T-maze behavior, and locomotor activity in an animal activity monitor.

The lesioned only female rats had striatal cell losses comparable to those seen in the lesioned males. In addition, they evidenced some similar behavioral deficits. They showed an impaired T-maze performance, and an amphetamine-induced hyperactivity, compared to controls. Conversely, the female rats appeared different from the males in that they were hyperactive in the animal activity monitor and gained weight following the lesions. Possible reasons for these differences include sex and strain effects. Finally, this experiment extended past work by finding that the lesioned rats were significantly impaired on a sensorimotor task compared to controls.

The neuronal cell loss caused by the lesion was partially reversed by the implants of fetal striatal tissue. In addition, two of the lesion-induced behavioral deficits (T-maze and spontaneous locomotion) were partially reversed by the transplants. These results suggest that the transplants integrated within the host brain, and influenced the behavior of the host animals. They suggest that the striatum is involved in the regulation of locomotor activity and in the regulation of the many processes that are required for successful T-maze performance.

BEHAVIORAL CONSEQUENCES OF KAINIC ACID LESIONS AND FETAL TRANSPLANTS OF THE STRIATUM

by

A. Wallace Deckel

Dissertation submitted to the Faculty of the Department of Medical Psychology
Graduate Program of the Uniformed Services University of the Health Sciences
in partial fulfillment of the requirements for the degree of Doctor of Philosophy
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ABBREVIATIONS USED

ANOVA.....ANALYSIS OF VARIANCE
C.....CENTIGRADE
cc.....CUBIC CENTIMETERS
DAB.....DIAMINOBENZIDINE
mm.....MILLIMETERS
NGS.....NORMAL GOAT SERUM
PBS.....PHOSPHATE BUFFERED SALINE
TBS.....TRIZMA BASE
TH.....TYROSINE HYDROXYLASE
u.....MICRONS
um.....MICROMETERS
ug.....MICROGRAMS

INTRODUCTION

Since the early 1970's, the use of kainic acid, an excitotoxin which destroys neuronal cell bodies while sparing fibers of passage, has been used as a tool to better understand biochemical and anatomical components of the striatum (Coyle, Schwarcz, Bennett, & Campochiaro, 1977; Coyle, 1983; McGeer & McGeer, 1976; Schwarcz & Coyle, 1977a; 1977b). While some have claimed that kainate striatal lesions represent an animal model of Huntington's Disease (see Appendix A for a review of Huntington's Disease, and the evidence that supports the use of kainic acid as a model for this disease), this is unproven.

Kainic acid striatal lesions have also been used to examine how the striatum regulates a variety of complex behaviors that involve learning and memory (Mason, Sanberg, & Fibiger, 1978a; 1978b; Pisa, Sanberg, & Fibiger, 1979; 1980; Sanberg, Pisa, & Fibiger, 1978; 1979a; 1979b; see also the complete review in the next section). However, its use to date has been rather limited. For example, previous experiments assessing behavioral consequences of striatal kainic acid lesions have been done on male rats of three strains, including Wistars, CYF, and Woodlyn. The effects of the lesion in other commonly used rat strains, including Sprague-Dawley rats, is not known. As strain differences have been observed to affect the pathological effects of kainic acid (Sanberg, Pisa, & McGeer, 1979), it is also possible that behavioral effects will vary as a function of strain. In addition, the behavioral deficits that result from kainic acid lesions have been assessed only over the short term. This is an important limitation, as work by

Whittier and Orr (1962) demonstrated that behavioral deficits in rats secondary to electrocoagulative lesions of the striatum disappeared 30 days after the lesion. It is unknown what the long term effects of striatal kainate lesions are.

The current experiments assessed the behavioral effects of striatal kainate lesions in a way that extends the current knowledge of this topic. It did so by using a different sex and strain than past experiments, and followed behavioral changes for longer time periods than had been done by others. In addition, this experiment coupled the use of kainic acid lesions with the use of fetal striatal implants to assess the ability of this procedure to reverse the deficits caused by the kainic acid lesions.

The research was composed of two experiments. The first experiment was a replication and extension of previous published work regarding the behavioral effects of kainate striatal lesions. Specifically, it examined the effects of kainic acid lesions of the striatum in male Wistar rats on a number of behaviors identified by others as being sensitive to the kainate lesions. These behaviors included spontaneous locomotion, locomotion in response to amphetamine administration, response to the convulsant metrazol, T-maze behavior, and body weight changes. Because all of the published literature on these measures except for T-maze has come out of the two laboratories of Fibiger and Mason (and their associates), an attempt to replicate their work in a different laboratory was thought to be worthwile.

In the second experiment, the behavioral effects of kainic acid lesions of the striatum in female Sprague-Dawley rats was assessed. It was useful to examine the effect of these lesions in female rats because it is unknown to what extent the neurological effects of kainic acid

lesions of the striatum will differ as a function of sex, and it is unknown if female rats show similar behavioral deficits to the males following the lesions. Additionally, the second experiment was intended to extend the current literature on the long term behavioral effects of kainic acid lesions of the striatum. To do so, the experiment assessed, at 90 days postsurgery, behavioral tasks that had been shown at times of less than one month post kainic acid lesion of the striatum to be changed by the lesion. Ninety days is a longer time postlesion than had previously been examined, and represents a period of time that allows for the fetal implants to fully mature (see the review on fetal transplants in Appendix B). Because the implants take 2-3 months to connect with their target tissue, it would not have been possible to examine their behavioral effects in this preparation before this time.

The behavioral measures used in the second experiment were used by other investigators working with this model, and included measures of delayed rewarded alternation, open field behavior, locomotor activity, convulsant activity, and weight changes. It was hypothesized that the results would extend the current literature by examining the effects of these lesions on these measures over a much longer time span than had been previously done.

Thirdly, a measure was added to the second experiment which had not been used by others to assess the behavioral deficits following kainic acid lesions of the striatum. Specifically, a neurological sensorimotor examination previously used to assess behavioral changes in rats with hypothalamic and nigro-striatal tract lesions was modified. This test was designed to assess rigidity, apraxia, arousal, and the ability to orient in the rats. Pilot testing had revealed that the entire examination, as described by Dunnett, Schmidt, Bjorklund,

Stenevi, and Iversen (1981), was not sensitive to the kainic acid lesion. For this reason, only that portion of the test shown during pilot testing to be sensitive to the lesion was used in the experiment.

Finally, the second experiment was conducted to assess the behavioral effects of fetal striatal implants placed in adult rats with kainic acid lesions of the striatum. There is a growing literature which suggests that fetal brain tissue implanted into adult recipients integrates into the host brain and assumes a role in the functioning of the animal. Because the implanted striatum grows well in adult rats with kainic acid lesions of the striatum (Deckel, Robinson, Coyle, & Sanberg, 1983; Deckel, Robinson, & Sanberg, 1983; Kimura et al., 1980; Schmidt et al., 1981), and because in other neural systems the implants behaviorally function in the recipient brain (see review in Appendix B), it was postulated that performing this manipulation would decrease the behavioral deficits that exist long term in the kainic acid lesioned rat.

In order to better present the rationale for the experiments, the next section will review previous work done on the effects of kainic acid striatal lesions, both from a bilological and behavioral viewpoint.

KAINIC ACID LESIONS OF THE STRIATUM

(i) BIOCHEMICAL/PATHOLOGICAL EFFECTS

Kainic acid lesions of the striatum in rats cause destruction of the neurons which receive glutamatergic projections from prefrontal

efferents (Divac, Markowitsch, & Pritzel, 1978). There are losses of intrinsic neurons, marked shrinkage of striatal tissue, glial proliferation in the lesioned area, and ventricular dilatation (Barbeau, 1973; Coyle, Schwarcz, Bennett, & Campochiaro, 1977; Lange, Thorner, Hopf, & Schroder, 1976; McGeer & McGeer, 1976; Roizin, Kaufman, Willson, Stellar, & Liu, 1976; Schwarcz & Coyle, 1977b). In addition, there is little disruption of axons of passage traveling through the lesioned area of the striatum (Coyle, Molliver, & Kuhar, 1978; Coyle, 1983; Divac et al., 1978; Dunnett & Iversen, 1981; Mason & Fibiger, 1979; Mason, Sanberg, & Fibiger, 1978a; Nadler, Perry, & Cotman, 1978; Schwob, Fuller, Price, & Olney, 1980).

There are also a number of biochemical changes following kainic acid striatal lesions. For example, there are decreases in striatal gaba-aminobutyric acid (GABA) and glutamic acid decarboxylase (GAD), and in choline acetyltransferase (ChAT), muscarinic receptor binding, angiotensin converting enzyme (ACE), and serotonin receptors (Coyle, Schwarcz, Bennett, & Campochiano, 1977; Divac et al., 1978; Fibiger, 1978; Mason, Sanberg, & Fibiger, 1978a; 1978b). Tyrosine hydroxylase and dopamine levels are relatively unaffected or moderately elevated in both conditions (Divac et al., 1978; Fibiger, 1978; Mason, Sanberg, & Fibiger, 1978a; 1978b). Thus there are many pathological and biochemical changes following striatal kainate lesions.

(ii) SPECIFIC BEHAVIORAL DEFICITS FOLLOWING KAINIC ACID STRIATAL LESIONS

(A) T-MAZE BEHAVIOR

A number of changes have been found in both spontaneous and

rewarded alternation tasks following kainic acid lesions of the dorsal striatum. Dunnett and Iversen (1981) found that, following dorsal but not ventral striatal lesions, rats given a choice of spontaneously alternating in a T-maze changed the direction of their side bias. That is, following surgery, rats that had initially alternated more often to the right arm of the maze now did so to the left arm, and vice versa, compared to controls. The degree of the bias (i.e.,how often the rat chose one arm over the other) did not change.

Pisa, Sanberg, and Fibiger (1980) trained rats somewhat differently on the T-maze. They employed a paradigm in which the animals were rewarded if they correctly alternated, whereas on the next trial they were allowed to spontaneously alternate, receiving no reward for a correct alternation. They found that the rats with the kainate striatal lesions ran more slowly than controls, independent of trial outcomes. Running latencies for both groups decreased with training, although they were significantly longer on nonrewarded than on rewarded trials. The control rats learned to alternate speed in both the early and the late trials of the reward alternation sequence. The lesioned rats, although alternating in early trials, failed to alternate during the late trials. They concluded that an increased susceptibility to interference (i.e., from one trial to the next) could account for the impaired alternation performance of the kainic acid lesioned rats in the later trial. Using a different rat strain, and a different T-maze procedure whereby rats were continuously reinforced on a spatial position habit, these authors (Pisa, Sanberg, & Fibiger, 1980) found no difference in speed of maze running. They speculated that lack of a memory component in this paradigm (i.e. rats did not need to recall if this was a rewarded or nonrewarded trial) accounted for the reported

difference between these findings and those of Pisa, Sanberg, and Fibiger (1979). Aside from the impaired rate of running for the kal group, Pisa, Sanberg, Corcoran, and Fibiger (1980) found no difference in the lesioned animals on the rate of extinction of T-maze alternation when the reward was removed. They did, however, find that the rats with the kainate lesions were significantly impaired compared to controls on the food-reinforced alternation trials. Others have found similar deficits in rewarded alternation following kainic acid lesions of the dorsal striatum. Pisa, Sanberg, and Fibiger (1978) found that all of their kainic acid treated rats failed to learn a food reinforced spatial alternation task. Divac et al. (1978) found that on 60 trials in a rewarded alternation task, dorsal striatal lesions lead to very large and persistent deficits on this task. Lesioned animals made a significantly greater number of errors on the postoperative trials compared to controls. Each of these studies employed postoperative periods of 3 weeks or less.

Thus, while the findings are somewhat inconsistent for spontaneous alternation, on food reinforced alternation trials, kainic acid lesions of the striatum lead to large and persistent deficits up to 3 weeks following surgery. This suggests that the lesioned rats have some disturbances, whether in short term memory, attention, arousal, etc, which interfere with their ability to successfully perform on the T-maze.

(B) LOCOMOTOR ACTIVITY

A number of authors have demonstrated that, for up to 3 weeks after kainic acid lesions of the dorsal striatum, there is no difference

in general daytime locomotor activity or rearing behavior (Dunnett & Iversen, 1981; Mason, Sanberg, & Fibiger, 1978a; 1978b; Sanberg, Pisa, & Fibiger, 1978). In contrast to these reports, Mason and Fibiger (1979) found that kainic acid lesions of the striatum in male Woodlyn rats caused increases in the nocturnal locomotor activity of the animals but did not affect daytime activity. In addition, Dunnett and Iversen (1981) found that, although there may be no difference in daytime locomotor activity in rats with kainic acid lesions when they are fed ad lib, food depriving the animals led to a significant hyperactivity.

Other changes in locomotor behavior also have been found. If the lesioned rats are placed in conditions that require them to locomote from one place to another (i.e., from one arm of the T-maze to another) animals with kainic acid lesions of the striatum show decreased activity (Sanberg, Pisa, & Fibiger, 1978) compared to controls. The mechanism of this decrease in activity is unknown. Sanberg, Pisa, and Fibiger (1978) chose to make a psychological interpretation of this observation, speculating that it was secondary to fear of novelty. They hypothesized that this led the rats to remain "frozen" in the arm of the maze, and thus led to a decrease in the locomotor activity. Such behavior has been previously characterized by Berlyne as being typical of fearful behavior in rats (Berlyne, Koenig, & Hirota, 1967).

A significant hyperactivity also can be induced in the kainic acid lesions animals by administration of the drug d-amphetamine (Fibiger, 1978; Mason, Sanberg, & Fibiger, 1978a; 1978b; Sanberg, Pisa, & Fibiger, 1979b). With i.p. administration of d-amphetamine sulfate, the kainic acid lesions animals show a marked increase in the onset, peak effect, and duration of effect of the drug (Fibiger, 1978). Amphetamine increases the availability of dopamine in the synaptic cleft

and, presumably because of receptor denervation sensitivity, causes an increased response to dopamine in the lesioned animals. To explain amphetamine's effect in the lesioned rat, Mason et al. postulated that a substantial portion of the striatonigral inhibitory feedback loop originates in the dorsal striatum. This region of the striatum sends inhibitory projections to the nucleus accumbens and ventral striatum. These two structures in turn project to the neocortex and modulate the primary motor output. The net result of lesioning the dorsal striatum is a disinhibition, or increased rate of firing, from the ventral striatum and nucleus accumbens in response to increased dopamine levels, as the negative feedback loop of this system is removed. Thus lesioning the dorsal striatum and administering d-amphetamine leads to an increased excitation in the nucleus accumbens and the ventral striatum and a subsequent increase in motor activity.

(C) CHANGES IN EATING BEHAVIOR

After kainic acid lesions of the dorsal striatum, male rats show a temporary aphagia, adipsia, and body weight reduction that lasts from 1-5 days postoperatively (Pettibone, Kaufman, Scally, Meyer, Ulus, & Wyatt, 1978; Sanberg & Fibiger, 1979; Sanberg, Pisa, & Fibiger, 1979a; 1979b; Sanberg, Pisa, & Fibiger, 1978). When the rats were able to freely feed again, their ad lib food and water intake did not differ from controls, and their rate of weight gain returned to a level comparable to that of the control group (Sanberg & Fibiger, 1979). However, the initial weight loss was not made up, and this weight loss led to a consistent weight difference between the lesioned rats and the controls 2 weeks after surgery.

While the amounts of ad lib eating and drinking did not differ between groups, non-prandial (i.e. drinking behavior in food deprived rats) drinking in rats with striatal lesions was significantly greater than in control rats (Sanberg & Fibiger, 1979). In addition, patterns of eating shortly after lesioning differed between groups. Lesioned rats chewed more pellets than controls, either because of decreased praxis (i.e., decreased ability to coordinate fine motor movements) immediately after surgery, or because of an increase in stereotypic movements (Sanberg & Fibiger, 1979; Sanberg, Pisa, & Fibiger, 1979a). Furthermore, it was found that anorexia induced by either d-amphetamine or fenfluramine was increased in rats with striatal kainic acid lesions (Sanberg & Fibiger, 1979), causing a greater reduction in food intake in the lesioned rats than in controls.

The temporary adipsia, aphagia, and loss of body weight seen in kainic acid lesions of the striatum is similar to that seen after electrolytic lesions of the lateral hypothalamus (LH) or nigro-striatal bundle (NSB) (Baez, Ahlskog, & Randall, 1977; Fibiger, Zis, & McGeer, 1973). However, in contradistinction to the kainic acid lesions of the striatum, LH and NSB lesions cause an increase in prandial drinking, an effect not seen in the lesioned animal. Furthermore, the increased amphetamine and fenfluramine anorexia seen in the striatally lesioned animal are not found in the LH and NSB lesions. Thus, there are both similarities and differences between LH, NSB, and striatal lesions and their effects on eating behaviors.

(D) SEIZURE ACTIVITY AFTER KAINIC ACID LESIONS OF THE STRIATUM

Peripheral, intercisternal, or intracerebral injections of kainic

acid precipitate a striking seizure disorder in the rat characterized by wet dog shakes, masticatory movements, rearing, forelimb clonus, and an occasional generalized tonic-clonic seizure (Coyle, 1983). After surgery, rats receiving kainic acid lesions of the striatum experience acute serial clonic convulsions, with later spontaneous recurrence of generalized seizures (Pisa, Sanberg, Corcoran, & Fibiger, 1980). In addition, when given pentylenetetrazol (an agent which experimentally induces seizures), lesioned animals showed a potentiation of the ensuing convulsions (Pisa, Sanberg, Corcoran, & Fibiger, 1980). These authors also found that immediately after kainic acid lesions, and lasting for 4-5 hours, the animals had repeated episodes of clonic jerking of the forepaws, and bouts of body circling. Spontaneous seizures continued to occur for the duration of their experiment (77 days), with the animals evidencing seizures several times during the course of a day for periods of 25-30 seconds each. The tonic phase of these seizures lasted for 5-6 seconds, and was followed by a series of rapid clonic jerks, involving first one, and then both, forepaws. Postictally, the rats were hyperactive, and demonstrated either increased aggressivity or increased flight responses.

Additionally, Pisa, Sanberg, and Fibiger (1980) gave pentylenetetrazol to rats with kainic acid lesions of the striatum 45 days after surgery. These animals showed intermittent myoclonic jerks of the body, which merged into clonic or tonic-clonic convulsions of the forelimbs. In comparison to the control group, the kainic acid lesioned rats showed significantly decreased latencies to the first ictal response, and significantly decreased latencies to the first generalized convulsion.

(E) OTHER BEHAVIORAL TASKS

When appetitive bar pressing behaviors have been examined in rats with kainic acid lesions of the striatum, no behavioral deficits have been noted (Fibiger, 1978; Pisa, Sanberg, & Fibiger, 1978; 1979; Sanberg, Pisa, & Fibiger, 1979a; 1979b). The kainic acid lesions do not interfere with either the asymptotic lever pressing performance or with the rate of acquisition of the task when reinforcement was continuous (Sanberg, Pisa, & Fibiger, 1979a; 1979b). However, the kainic acid lesioned rats do respond significantly more during extinction trials on a crf bar pressing schedule (Fibiger, 1978; Sanberg, Pisa, & Fibiger, 1979b). This impairment of extinction is not seen on all tasks. Rats with kainic acid lesions of the dorsal striatum do habitute at a normal rate on a task of partially reinforced T-maze running (Pisa, Sanberg, & Fibiger, 1978). In addition, the animals show no changes in spontaneous locomotor activity. On a passive-avoidance task, they step down from a platform at the same rate as controls do, and respond as quickly as controls in flinching, jumping, and vocalizing after administration of shock (Fibiger, 1978). However, they do take significantly longer to learn to avoid the shock (Fibiger, 1978; Sanberg, Pisa, & Fibiger, 1979b; Sanberg, Lehmann, & Fibiger, 1978). In addition, the lesioned animals take significantly longer to learn not to step off the protected platform. They also stepped off the platform onto the electrified grid more often than controls (Sanberg, Lehmann, & Fibiger, 1978). Thus on tests of extinction from a continuous reinforcement schedule of bar pressing, on a passive-avoidance paradigm, and on rewarded alternation, the kal animals show a number of impairments that point to a number of deficits that surface in some, but not all, learning tasks.

EXPERIMENT ONE

EXPERIMENT ONE

(i) GENERAL OUTLINE OF EXPERIMENT ONE

This experiment examined the effects of kainic acid lesions of the striatum in male Wistar rats on a number of behaviors identified by others as being sensitive to the kainate lesions, including T-maze behavior (Divac et al., 1978; Dunnett & Iversen, 1981; Pisa et al., 1979; Pisa, Sanberg, & Fibiger, 1980; Sanberg, Lehmann, & Fibiger, 1978), spontaneous and amphetamine affected locomotor activity (Fibiger, 1978; Mason & Fibiger, 1979; Mason et al., 1978a; 1978b; Sanberg, Pisa, & Fibiger, 1978; 1979a), body weight changes (Sanberg & Fibiger, 1979; Sanberg, Pisa, & Fibiger, 1979b), and seizure activity in response to the convulsant metrazol (Pisa, Sanberg, Corcoran, & Fibiger, 1980). Because all of the published literature on these measures, except for T-maze, had come out of the two laboratories of Fibiger and Mason (and their associates), this experiment represented an attempt to replicate and extend their work in a different laboratory. The tasks used, time course of the experiment, type and location of the lesion, etc., were based on published reports of others.

After handling and being reduced to 85% of their ad lib body weight, male Wistar rats were trained to criteria on a T-maze (i.e. alternating 85% or better for three consecutive sessions). They were then fed ad lib for 3 days, weighed, and underwent surgical lesioning. For the rest of the experiment, animals were weighed each morning. Starting on day 11, they were again reduced to 85% of their body weight

over the course of 5 days, and rerun twice daily on the T-maze for 10 sessions (i.e. a total of 200 possible alternations). Following completion of the T-maze task, the rats were given free access to food, and 2 days later assessed for spontaneous locomotor activity. They were placed in an animal activity monitor (Omnitech, Columbus, Ohio--Model DCM-8) during the middle of their light cycle, and assessed in 10 minute time blocks over the course of 2 hours. The locomotor activity assessed included bouts of movements, time spent moving, bouts of rearing, time spent rearing, bouts of movements in the horizontal direction, total distance traveled, total time spent resting, bouts of stereotyped movement, and time spent moving in a stereotypical manner. Pilot testing had shown that this method of testing reliably discriminated lesioned from control animals---lesioned animals habituated to the novelty of the open field slower than did controls, and remained hyperactive throughout the middle portion of the testing time.

Immediately upon completion of their two hours in the open field, the animals were given amphetamine injections (1.0 mg/kg/2 cc water i.p., based on results from pilot testing), and were reassessed on these same measures in 10 minute time blocks over the course of one hour. Twenty four hours after the completion of this task, animals were then given an injection of a convulsant (metrazol, 0.70 mg/kg/1 cc water, s.c.) and the time to the first ictal response and first grand mal seizure (as described by Pisa, Sanberg, Corcoran, & Fibiger, 1980) was recorded. After initiation of the first grand mal seizure, the animals were anesthesized, perfused, and the brains taken for histological examination of the striatum, hippocampus, amygdala, ventromedial hypothalamus (VMH), and pyriform cortex.

(ii) METHODS: EXPERIMENT ONE

(a) SUBJECTS

To replicate previous work, the same sex and strain rat as used by other investigators (Divac et al., 1978; Mason et al., 1978a; 1978b; Pisa et al., 1979; Sanberg & Pisa 1979; Sanberg, Lehmann, & Fibiger, 1978; Sanberg, Pisa, & Fibiger, 1978; Sanberg et al., 1979a; 1979b; Sanberg, Pisa, & McGeer, 1979) was employed for this experiment. Specifically, young adult male Wistar rats, weighing between 225 and 250 grams at the start of the experiment were used. They were housed according to the methods of Sanberg et al. (1979a; 1979b); i.e., they were maintained on a 12 hour light/dark cycle and housed one to a cage throughout the course of the experiment. Cages were constructed of clear polypropylene 10"x18"x8". Animals were maintained at a constant temperature (68 degrees Fahrenheit) and humidity (40%), and had constant access to water and Purina rat chow pellets.

Two sets of animals, including a sham lesioned and kainic acid lesioned group, were used. Eight animals (the number of animals commonly reported by other investigators in this field) in each group underwent surgery. All animals were assessed in the activity monitors for both spontaneous and amphetamine affected locomotor behavior, for response to the convulsant metrazol, and for weight changes after surgery. Although eight animals per group were started on the T-maze testing, three animals in each cell were removed because of their failure to seek and eat the food pellets. Thus five animals per group were assessed on the T-maze. Pilot testing with female Sprague-Dawley

rats with identical kainic acid lesions of the striatum had shown this lesion to cause a large impairment in the ability of these animals to alternate in a rewarded alternation paradigm sufficient to result in statistically different performances on this task with only three animals per group.

(b) SURGERY

Kainic acid lesions of the anterior medial striatum were performed according to the methodology of Divac et al. (1978). All surgery was done with animals under i.p. pentobarbital/chloral hydrate (chloropent, Fort Dodge, Indiana) anesthesia (0.30 ml/100 gms). The kainic acid solution (0.8 ug kainic acid delivered in 0.4 ul of phosphate buffered saline, ph 7.4) was always prepared fresh. Pilot testing was done to determine the amount and rate of kainic acid to be used for the experiment. Animals received 0.4 ul of the kainic acid solution bilaterally in each striatum. The coordinates from bregma were; A 1.5mm, L 2.2mm, and H 4.5mm. The kainic acid was delivered in a 5 ul Hamilton syringe at a rate of 0.1 ul/90 seconds, and the needle was retracted 100 um and left in place for 30 seconds after completion of the injection to prevent leakage of the solution to the cortex through the needle tract. The left striatum was lesioned first, followed by the right, to ensure standardized treatment of all animals. The particular region of the striatum chosen for lesioning was decided on because: (1) it was the same coordinates employed by Divac et al. (1978), (2) it was similar to coordinates used by other investigators assessing behavioral effects of kainic acid lesions (Dunnett & Iversen, 1981; Fibiger, 1978; Pisa et al., 1979; Mason et al., 1978a; 1978b; Sanberg, Pisa, & Fibiger,

1979; Sanberg & Fibiger, 1979; Sanberg, Lehmann, & Fibiger, 1978), (3) more posterior striatal lesions led to fatal adipsia and aphagia (Divac et al., 1978), and (4) the pathophysiological changes after lesions in this area have been described as being similar to those seen in HD (Coyle et al., 1977; Coyle, McGeer, McGeer, & Schwarcz, 1978; Fibiger, 1978; McGeer & McGeer, 1976; 1978).

(iii) BEHAVIORAL TESTING

(a) DELAYED REWARDED ALTERNATION

A T-maze of conventional design, with wood floors and walls painted flat gray, was used for behavioral testing at ground level. The starting arm was 21 inches long, with each side arm 20 inches long. The starting ally and each side arm had a sliding guillotine wood door. The floor was 5 inches wide, and the walls 12 inches high throughout. Holes were drilled as food cups in the ends of each side arm, and 180 mg food pellets (P.J. Noyes Co) were used as food reinforcement.

After 3 days of handling to gentle them, the rats were trained in delayed rewarded alternation, following the paradigm of Divac et al., (1978), and Wikmark, Divac, and Weiss (1973). After completion of the gentling procedure, the animals were weighed and then food deprived to 85% of their ad lib body weight. Once they reached this weight, training began. On the first 2 days of training the guillotine doors were removed, both arms were baited, and 10 pellets were scattered throughout the maze. Each rat was left in the maze for at least 10 minutes. On the third day of training the door was introduced, and rats were reinforced only when they ran to the food cup in the end of the

side arm. When an animal had completed 21 consecutive trials in 30 minutes, formal training was started.

Twenty-one trials were done twice daily, once in the morning and once in the afternoon. On the initial trial, both sides were baited. On each of the remaining trials the animal was rewarded for entering that side which was not visited on the previous run. In other words, one arm was baited until responded to, and the rats were rewarded only when alternating. Following a response, the animal was moved to the home cage for approximately 15 seconds, returned to the maze, and immediately released. Rats were trained until they reached a criteria of 85% successful alternation (three errors) or better on three consecutive sessions. This ensured that all animals were alternating at an equivalent rate on the T-maze by the end of the presurgery training period. To ensure that experimental groups were not different, animals were assigned to experimental groups based on the number of trials required to reach this presurgery T-maze criteria.

At 10 days postsurgery or sham surgery, the animals were reduced to 85% of their ad lib body weight. Once they achieved this weight, they were immediately started in the rewarded alternation paradigm. As before, 21 trials were given twice daily, using the paradigm described above. Because rats with kainic acid lesions of the striatum do not learn to alternate even after 400 trials (Divac et al., 1978), animals were not run to criteria on the postlesion measure. Rather, they were run for 10 days, for a total of 200 trials of possible rewarded alternation.

From this measure, the number of correct alternations per animal per day were collected for 10 consecutive days. In addition, the number of isolated, and consecutive mistakes (perseverations) per animal per

day were recorded. A perseveration was counted each time an animal alternated to the same arm in the maze on three consecutive trials in a row (i.e., one alternation represents a correct response, one alternation followed by a nonalternation represents a correct alternation and then a mistake on the T-maze, and three consecutive visits to the same arm of the maze represents one correct response, one mistake, and one perseveration), according to the methodology of Dunnett, Bjorklund, Stenevi, and Iversen (1981).

(b) EVALUATION OF LOCOMOTOR ACTIVITY

Locomotor activity was measured via the use of an activity monitor. The animal activity monitor (Omnitech Corporation, Columbus, Ohio--Model DCM-8) consists of an open field surronded by plexiglass walls 16" x 16" x 12" with horizontal and vertical movement sensors. The apparatus utilizes a total of 45 high resolution infrared photocell beams, spaced one inch apart, and 24 low resolution beams, spaced 2 inches apart. The horizontal movement sensor consists of 4 pieces each which direct 8 photocell beams from front to back, and 8 photocell beams from side to side. Interruption of any of these beams leads to an increase in the horizontal counter read out. There are 8 beams in each of 2 vertical activity sensors that extend approximately 4 inches off the floor of the monitor. When any of the beams are interrupted, the vertical counter is incremented by one.

The monitor is interfaced with an Apple II+ computer. At the end of each 10 minute period, the accumulated data is stored, and data for the next 10 minutes is gathered. The measurements made by the activity monitors include:

1) horizontal activity---the total number of beam interruptions that occurred in the horizontal sensors,

2) vertical activity---the total number of beam interruptions that occurred in the vertical sensor during a given sample period,

3) total distance---distance travelled by an animal, in inches, during a 10 minute period,

4) rest time---computed by the monitor by subtracting time spent moving from the 10 minute interval,

5) stereotypical movement time---the time spent breaking the same beam repeatedly, accumulated for various beams during the 10 minute interval,

6) vertical time---when the animal activates the vertical sensors by rearing, this parameter starts incrementing and continues to do so until the animal goes below the level of the vertical sensor,

7) movement time---as long as the animal is moving (as measured by interruptions of different photocell beams) this parameter is incremented. When the animal takes longer than 1 second to move, this parameter is stopped until the next photocell is broken. Thus this measure corresponds to the amount of time the animal was in motion during a given sample period,

8) number of stereotypical movements---the number of times the monitor observed stereotypic behavior in the animal, as measured by repeated breakings of the same photocell beam, with a break of one second or more separating one stereotypic movement from the next,

9) number of vertical movements---each time the animal rears, this parameter is increased by one. The animal must go below the level of the vertical sensor for at least one second before the next rear can be registered,

10) number of movements---each time a movement is registered by a photocell interruption, separated by at least one second, this parameter is increased by one.

To extend previous work that used less sophisticated activity monitors (Fibiger, 1978; Mason et al., 1978a; 1978b; Mason & Fibiger, 1978; Sanberg, Pisa, & Fibiger, 1978; Sanberg, Lehmann, & Fibiger, 1978), animals were placed in the activity monitors at 3 weeks postsurgery and monitored for 2 hours. Two hours was chosen because pilot work had shown there to be (in Sprague-Dawley female rats with identical lesions) a hyperactivity in the lesioned animals from 30-90 minutes in the apparatus in comparison to controls, possibly due to a deficit in habituation to the novelty of the field by the animals. Specifically, between 11 am and 2 pm, animals were placed individually in the observation boxes of the monitor. They were left alone and quiet in the room for 2 hours observation. They then were removed, given 1 mg/kg of d-amphetamine sulfate i.p., according to the methodology of others (Fibiger, 1978; Mason et al., 1978a; 1978b; Mason & Sanberg, 1978) and observed for an additional hour. Information regarding their behavior for each 10 minutes in the apparatus was generated and compared.

(c) METRAZOL INDUCED CONVULSANT ACTIVITY

To assess seizure threshold in the animals, the convulsant metrazol was used according to the methodology of Pisa et al. (1980). After completion of the postlesion T-maze running at 2 1/2 weeks, rats were given at least 3 days of ad lib feeding in order to allow them to

return to body weight. The metrazol injection is a stressful procedure which, during pilot testing, led to the premature death of several animals due to postseizure anoxia. Thus experimental animals were given metrazol only when they were back at ad lib body weight (i.e. 3 days) and were, presumably, in physically better shape to survive the seizure. The rats received 70 mg/kg subcutaneous metrazol, a dose previously reported to cause generalized convulsions in most animals (Pisa, Sanberg, & Corcoran, 1980). In accordance with the findings of Pisa et al. (1980), two measures were obtained after injection: (i) latency to first ictal response (i.e., either a myoclonic jerk or a clonic convulsion), and (ii) latency to the first generalized convulsion (the point where the rat arches its back, and then begins a series of rapid clonic jerks with an eventual loss of consciousness).

(iv) HISTOLOGY

After kainic acid lesions of the striatum, cell damage has been reported in various other regions of the brain, presumably because of the distant excitotoxic effects of the rapidly discharging striatal cells. Other areas noted to be lesioned include the hippocampus, pyriform cortex, cerebellum, and amygdala (Coyle, Mollier, & Kuhar, 1978; Olney & deGubareff, 1978; Pisa et al., 1980; Wuerthele, Lovell, Jones, & Moore, 1978). For that reason, cell counts were done in the following regions (Konig and Klippel, 1967); striatum rostrally (8920u), caudally (7890u), and centrally to these two sites (8280u), pyriform cortex (8280u), amygdala (7020u), and dorsal hippocampus (regio inferior, 3430u). Five cell fields per area were counted under high magnification (1000x), averaged, and tallied.

The tissue preparation and basic staining techniques used were adopted from the methods of Clark (1978). Three rats per cell were anesthesized and perfused transcardially with phosphate buffered saline and 10% buffered formalin. The remaining five animals per cell were not perfused at this time, due to their involvement in a long term follow up of the effects of the lesion on weight. They were to undergo histology at a later date, and were not included for histology in the present experiment. The brains were removed and stored for at least 3 days in the buffered 10% formalin, then in a 10% formalin/sucrose solution for at least another 3 days. Slices of brain 30um thick were cut on a freezing microtome, and every fifth slice was mounted and stained with 0.1% cresyl violet.

(v) RESULTS

SUMMARY OF ANALYSIS STRATEGY

To analyze the data from the spontaneous locomotor activity measure, the amphetamine affected locomotor behavior, the T-maze, and the weight changes, a repeated measures ANOVA was done, in which the effect of the lesion was compared against controls over the time course of the experiment (Kirk, 1968). From this, three overall tests of significance were obtained, including: 1) between subjects, 2) repeated measures effect, and 3) interaction effect. When significance was detected, Tukey ratio t-test comparisons were made between the lesion and control groups. These ratios were adopted because they were suggested by Kirk (1968) as the appropriate comparison for this analysis.

(a) SPONTANEOUS LOCOMOTOR ACTIVITY

Three weeks after lesioning/sham lesioning, eight rats per cell were placed in the activity monitor for a 2 hour period. For each animal, ten different types of spontaneous locomotor behavior were counted and recorded over twelve intervals, each of 10 minute lengths. For each measure of spontaneous locomotion, there was no difference between lesioned and control animals. The graphs and ANOVA summary for each of these measurements are presented in Appendix C.

(b) AMPHETAMINE-INDUCED LOCOMOTOR ACTIVITY

Immediately after the rats had completed the 2 hour assessment of spontaneous locomotor activity in the animal activity monitor, they were injected with amphetamine (1.0 mg/kg/2 cc's H2O i.p.) and placed back in the monitor for 60 minutes. Locomotor activity was assessed exactly as reported on the spontaneous locomotor measures, with the exception that only six sets of 10 minute time intervals were measured.

As on spontaneous locomotor activity, for each of these measures an ANOVA with six repeated measures (Kirk, 1968) was done, giving three overall tests of significance. These included a between subjects (to test for group effect), a repeated measures (to test for changes due to time spent in the monitor), and an interaction effect (to test for the group effect at discrete time intervals). When there was statistical significance on the interaction effects, post-hoc Tukey ratio t-test comparisons were done to assess differences between the two groups at each of the six different time intervals per activity. They were chosen

because they are a more conservative test of significant differences than apriori comparisons. This computation was done according to the methods of Kirk (1968, p. 268-269).

Although eight rats per group were run on these measures, the data from one animal in the kainic acid group was lost due to an electronic error in the activity monitor. For that reason, only seven animals in the kainic acid lesioned group were included for analysis.

(1) HORIZONTAL ACTIVITY

Horizontal activity was significantly different between groups ($p=.023$). As shown in Figure 1, kainic acid lesioned animals were more active than controls at minutes 20-30 and 40-50 ($p<.05$). In addition, the repeated measures within groups effect was highly significant ($p<.001$) indicating that the animals significantly increased their activity as time progressed. The analysis of variance summary is presented in Table 1.

(2) TOTAL DISTANCE

Results on this measure were similar to those found on horizontal activity. As Table 2 illustrates, the lesioned group moved significantly more inches than controls at minutes 20-30 and 40-50 ($p<.05$). This is shown in Figure 2. Furthermore, the repeated measures (time in monitor) effect was significant ($p<.001$), indicating that the animals were more active as they spent progressively more time in the monitor.

TABLE 1: HORIZONTAL MOVEMENTS
(UNWEIGHTED MEANS SOLUTION)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	12731139.600	1	12731139.600	6.436	.023
ERROR	25716812.600	13	1978216.360		
WITHIN SUBJECTS					
TIME IN MONITOR	8323051.51	5	1664610.300	5.268	<.001
LESION X TIME	2060158.220	5	412031.644	1.304	.272
ERROR	20537312.700				

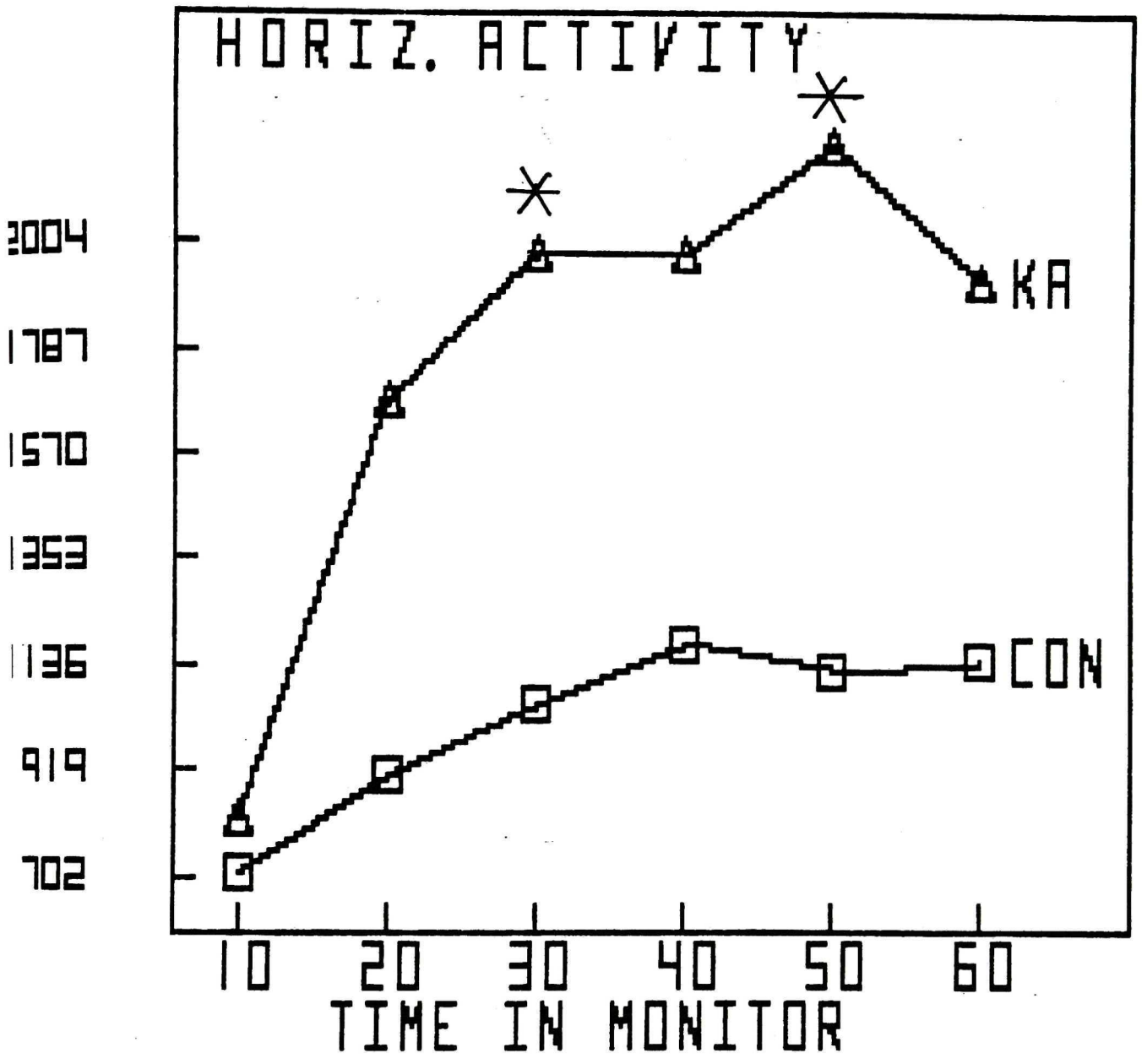


Figure 1: Mean number of horizontal movements emitted by the 2 groups of male Wistar rats is displayed during the 60 minutes after injection of d-amphetamine sulfate. Squares represent sham lesioned controls; triangles are kainic acid lesioned rats. * = $p < .05$;

TABLE 2: TOTAL DISTANCE (INCHES)
(UNWEIGHTED-MEANS SOLUTION)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	5393473.400	1	5393473.400	8.347	.012
ERROR	8399671.410	13	646128.57		
WITHIN SUBJECTS					
TIME IN MONITOR	2552770.50	5	510554.100	5.176	<.001
LESION X TIME	631439.798	5	126287.960	1.280	.282
ERROR	6411736.860	65	98642.106		

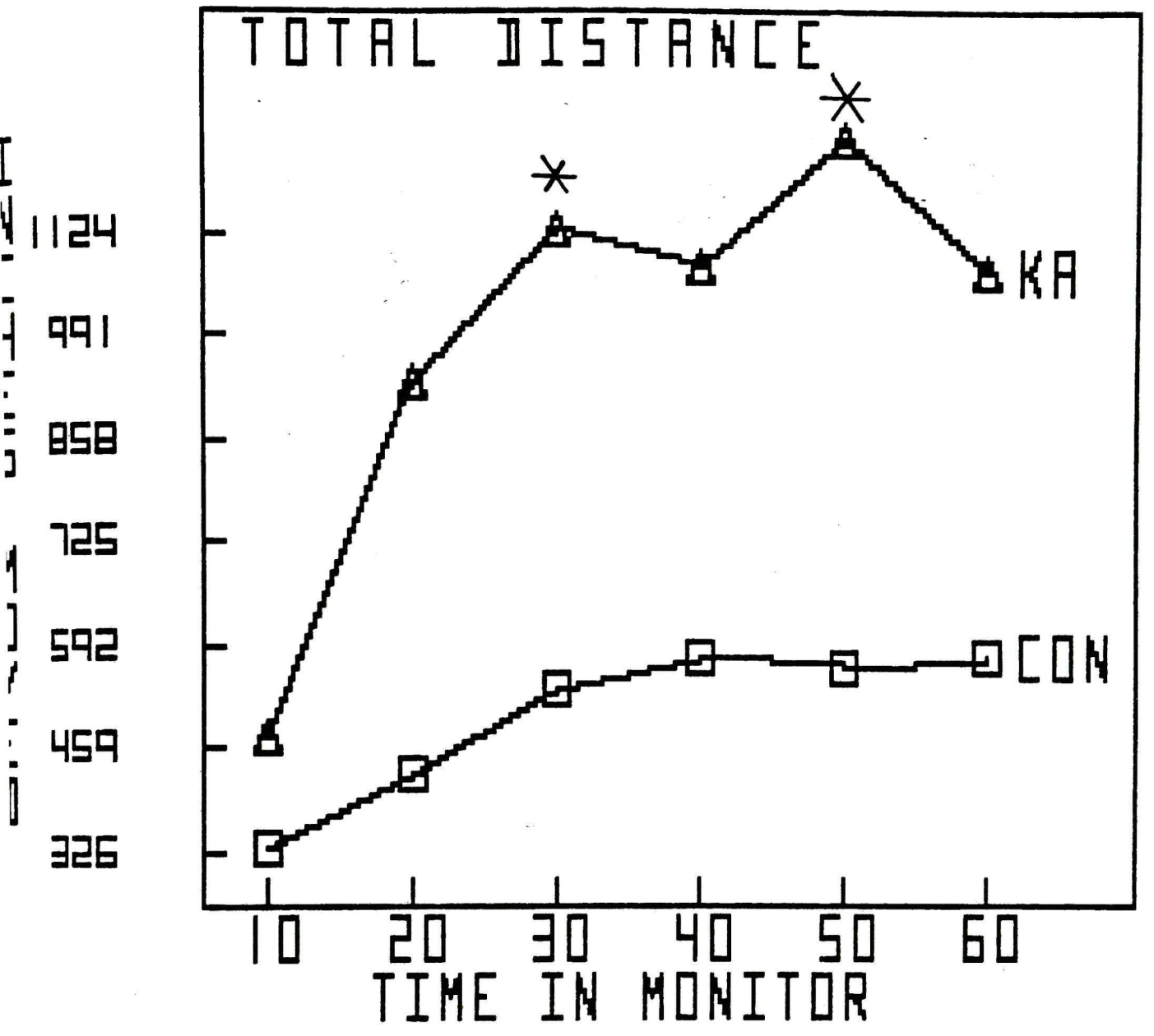


Figure 2: This figure shows total distance moved in inches by each of the 2 groups of animals for the 60 minutes after they received their amphetamine injections. Squares represent sham lesioned controls; triangles are kainic acid lesioned rats. * = $p < .05$;

(3) NUMBER OF MOVEMENTS

As Table 3 shows, control rats had significantly more discrete periods of movements than lesioned animals ($p=.012$). Figure 3 shows that this effect was significant for three of the time intervals.

When these results are considered together with the findings from the horizontal activity measure, it becomes apparent that the lesioned rats must have moved for most of their time in the monitor, whereas control rats must have moved for shorter periods, separated by frequent stops. This explanation accounts both for the higher horizontal activity emitted by lesioned rats, as well as their fewer discrete movement periods---i.e. they were moving virtually all the time. This explanation predicts that the time spent moving by the lesioned rats must have been greater than the time spent moving by controls.

(4) NONSIGNIFICANT FINDINGS

Consistent with the results from movement time, lesioned rats on the average spent less time resting than controls, and more time moving, although this effect was nonsignificant for both measurements. Only the time in monitor repeated measures effect was significant for both measurements, indicating that rest time decreased, and movement time increased, for the first 40 minutes the rats were in the monitor. The graphs and ANOVA tables are presented in Appendix D.

For the 3 vertical and 2 stereotypical movement measurements, there was no significant difference between groups for any of the between subjects or interaction effects. Thus on vertical movements,

TABLE 3: NUMBER OF MOVEMENTS AFTER AMPHETAMINE ADMINISTRATION (UNWEIGHTED-MEANS SOLUTION)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	5583.934	1	5583.934	9.227	.009
ERROR	7867.622	13	605.202		
WITHIN SUBJECTS					
TIME IN MONITOR	474.542	5	94.908	.801	
LESION X TIME	391.741	5	78.348	.661	
ERROR	7701.503	65	118.485		

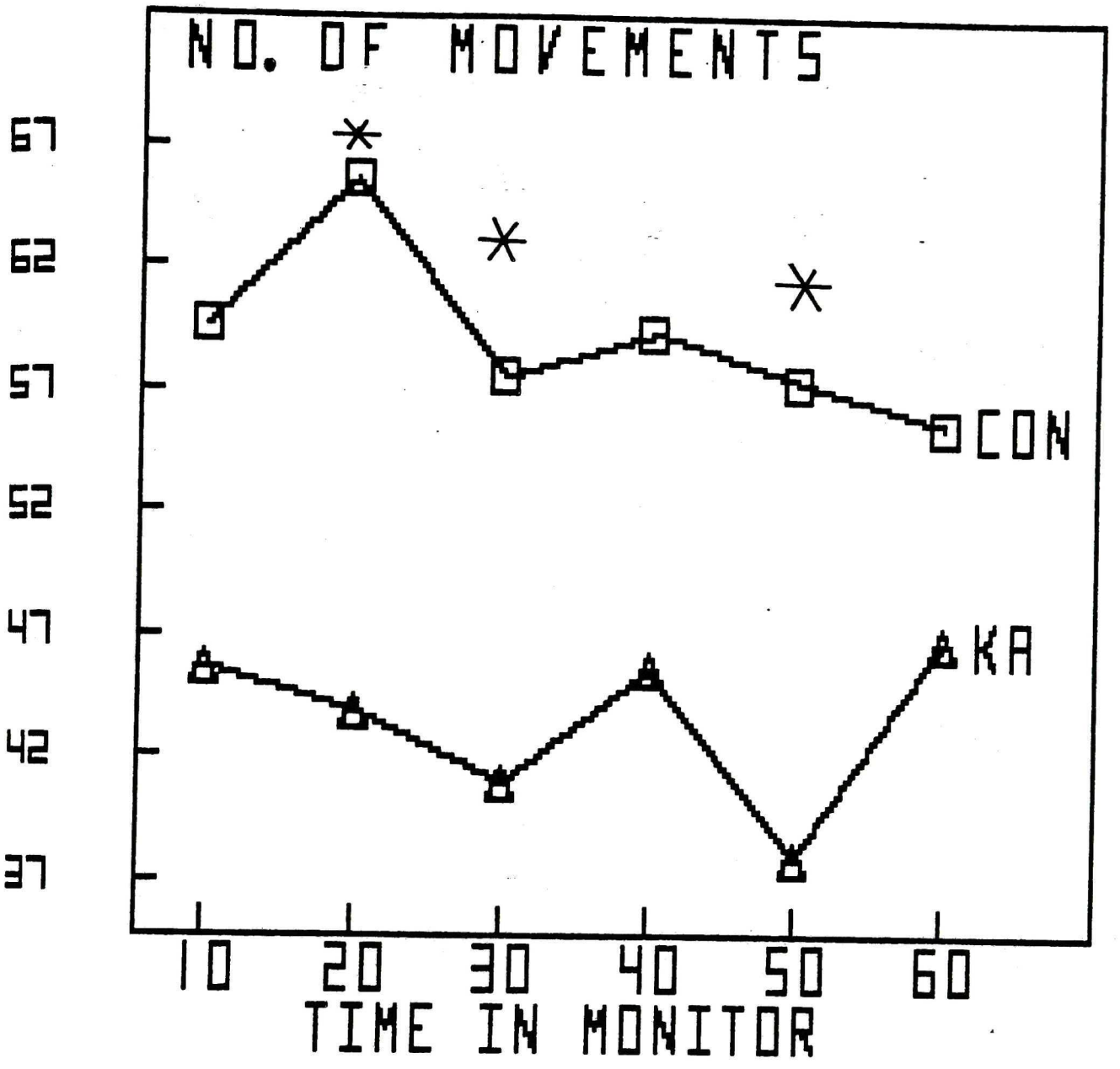


Figure 3: This graph shows mean number of movements emitted by the male Wistar rats over the 60 minutes after they received injections of amphetamine. Squares represent sham lesioned controls; triangles are kainic acid lesioned animals. * = $p < .05$;

vertical rears, time spent moving in the vertical plane, stereotypical movements, and time spent moving in a stereotypical fashion, there were no differences between the lesioned and control animals. The graphs and ANOVA tables from these measures are presented in Appendix D.

(5) SUMMARY

In summary, after amphetamine injection, the lesioned animals were hyperactive compared to controls on three measures of activity in the horizontal plane, including total distance travelled, horizontal activity, and number of bouts of movements in the horizontal plane. There were no significant differences between groups either on movements in the vertical plane or on stereotypical movements.

(c) BODY WEIGHT CHANGES

For the 10 days following surgery, up until the time they began food deprivation for the T-maze, rats were weighed at 8 am each morning. First, an ANOVA with ten repeated measures was done on the raw weights to assess if the two groups differed in their weights over the course of the experiment. As Figure 4 demonstrates, the lesioned group weighed, on the average, approximately 20 grams more than the control group prior to surgery. As an ANOVA on the raw weight scores revealed no between group or interaction effect, change scores were computed to compensate for the initial differences in weights. The results of the analysis are reported in Table 4. While the between group effect was not significant, both the repeated measure and interaction effects were significant at $p<.001$. Figure 5 shows the weight change scores plotted

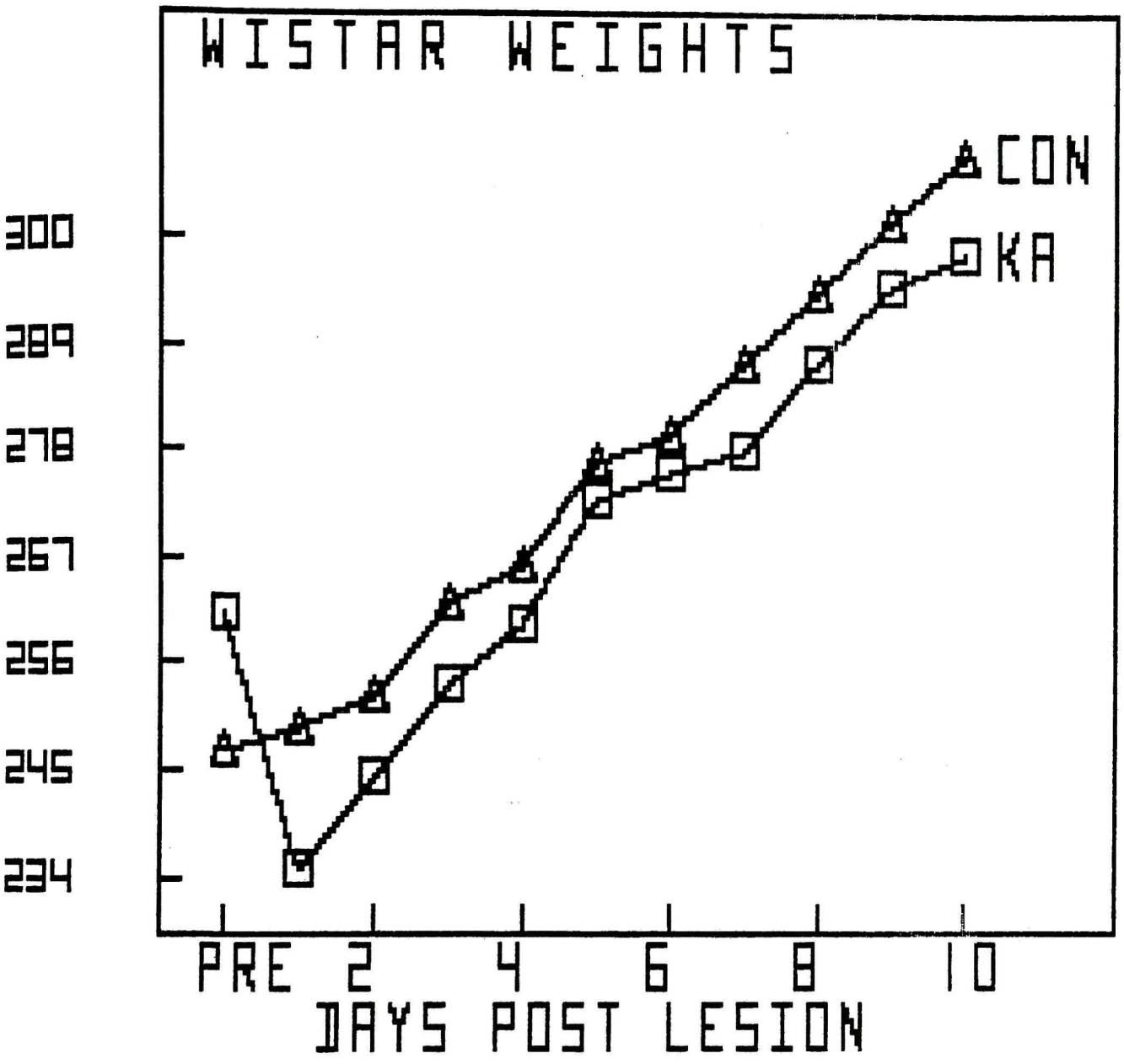


Figure 4: **Average weights for male Wistar rats** taken pre, and 10 days post, **kainic acid surgery.** **Squares** represent lesioned animals; upward pointing triangles are controls.

TABLE 4: WISTAR WEIGHT CHANGES (GRAMS)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	4473.225	1	4473.225	2.250	.153
ERROR	27835.150	14	1988.225		
WITHIN SUBJECTS					
DAYS	79145.375	9	8793.931	172.066	.001
LESION X DAYS	1961.025	9	217.892	4.263	.001
ERROR	6439.600	126	51.108		

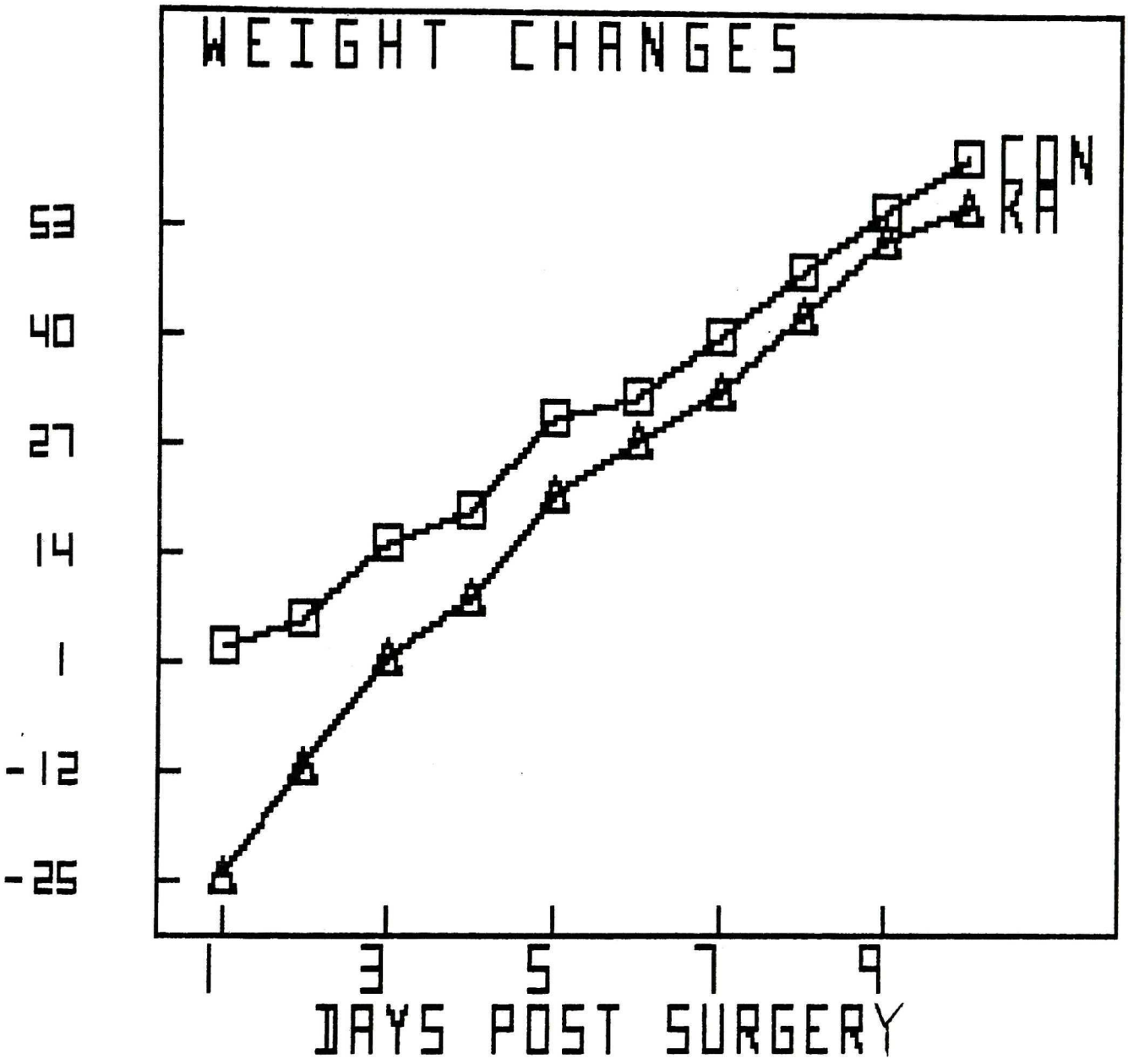


Figure 5: Weight changes in male Wistar rats computed by subtracting pre from post surgery weights for 10 days after surgery. Squares represent lesioned animals; upward pointing triangles are controls.

for the 10 days following surgery. Post-hoc interaction comparisons revealed that only the 25 gram difference at day one postsurgery was significant, indicating that the weight loss caused by the lesion was only temporary.

Experimental rats continued to gain weight more rapidly than controls for the 5 days following surgery. This rate slowed so that, after 5 days, lesioned rats maintained weight gains that paralleled controls. They persisted, however, with a consistent 3-6 gram weight loss relative to controls.

Thus the lesioned rats experienced a temporary weight loss which rapidly disappeared over the 5 days after surgery. Although the weight loss was statistically different only at day one postsurgery, on the average the lesioned rats never fully recovered over the 10 days after surgery, with experimental rats maintaining a small but persistent lower body weight than controls.

(d) T-MAZE RESULTS

Prior to surgery, rats were run twice daily for 20 trials per session in a delayed, rewarded alternation paradigm. They were trained until they alternated 85% (i.e. 17 times) or better for 3 consecutive days. Number of trials to criteria were computed by adding together the total number of completed daily sessions for each animal. A Student's t-test revealed that there were no significant differences between groups presurgery, as illustrated in Table 5 (a Mann Whitney U test was run on these data, also indicating no significant difference).

TABLE 5: TRIALS TO CRITERIA

	MEAN	S.D.
LESIONED	13.5	4.60
CONTROL	17.5	1.73

t=1.64; 8 d.f.

p= n.s.

Ten days postsurgery, the animals were again reduced to 85% of their ad lib weight, and rerun in the maze for ten additional 20 trial sessions. Two sessions were given daily for 5 days. For each session, the number of correct alternations were recorded. A two factor ANOVA with ten repeated measures was performed on this data. As shown in Table 6, both between subjects ($p<.005$) and the repeated measures ($p<.001$) effects were significant. Post-hoc interaction Tukey t-test ratios were done on a session by session basis to determine differences in performance between groups over the ten sessions. The computation was done according to the formula developed by Kirk (1968, 268-269).

Figure 6 displays the findings on this measure. The control animals performed significantly better than the lesioned animals on each of the ten postsurgery maze sessions. This difference reached the $p<.005$ level at sessions 2 and 5, the $p<.01$ level at sessions 3, 4, 6,

TABLE 6: T-MAZE RESPONSE
CORRECT ALTERNATIONS

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	568.427	1	568.427	13.995	.005
ERROR	324.933	8	40.617		
WITHIN SUBJECTS					
SESSIONS	198.073	9	22.008	4.533	.001
LESION X SESSIONS	58.873	9	6.541	1.347	.228
ERROR	349.567	72	4.855		

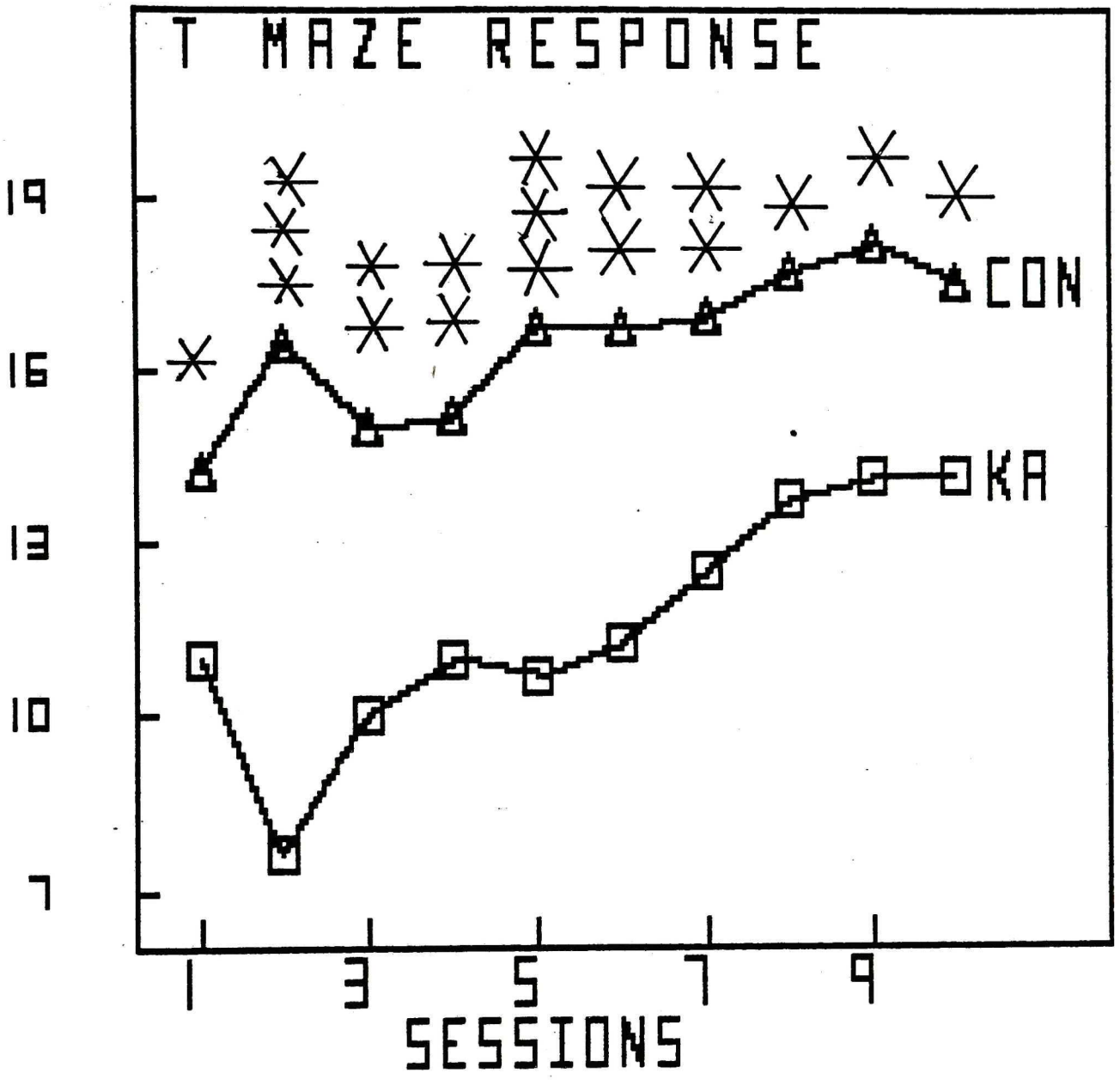


Figure 6: Average number of correct alternations (out of a possible 20) emitted by each group during the 10 sessions of post surgery T-maze running. Lesioned animals are represented by squares; controls are triangles. *=p<.05, **=p<.01, ***=p<.005.

and 7, and the $p<.05$ level at sessions 1, 8, 9, and 10.

Both groups of animals performed significantly better on the maze over the ten postsurgery sessions ($p<.001$). Starting at session 2, the lesioned animals showed a steady increase in the number of correct alternations, going on the average from 8 correct alternations per session to 14 by the tenth session. Figure 6 illustrates that the lesioned animals relearned the maze task at a rate that equaled or slightly exceeded that of controls.

During each session, the perseverative responses of individual animals were counted by recording the number of times three consecutive visits to one side of the maze were made. The total number of perseverations each animal ran were cumulated for the 10 sessions, and means and standard deviations were computed, as shown in Table 7.

TABLE 7: TOTAL PERSEVERATIONS

	MEAN	S.D.
LESIONED	33.3	20.35
CONTROL	4.5	2.89

Because of the large variance, a Mann Whitney U test was run, indicating that the lesioned animals perseverated significantly more ($p<.005$) often than controls (a Student's t-test was also done, indicating significance at the $p<.05$ level).

In summary, while there were no differences between groups prior to surgery, kainic acid striatal lesions led to severe and persistent deficits on the maze that caused the lesioned rats to make more mistakes than controls for each of the ten postsurgery sessions. In addition, lesioned animals perseverated more often than controls. However, the lesions did not prevent lesioned animals from relearning the paradigm at a rate that was at least equal to that of controls.

(e) PENTYLENETETRAZOL RESULTS

After completion of the postlesion T-maze running at 2 1/2 weeks, rats were given 5-7 days of ad lib feeding, and then were run in the animal activity monitor. Twenty four hours later, immediately before sacrifice, the convulsant pentylenetetrazol was injected. The rats received a subcutaneous dose of 70 mg/kg, according to the methodology of Pisa et al. (1980). Over the next 20 minutes, two measures were recorded, including latency to the first ictal response, and latency to the first grand mal seizure, as described in detail below. Animals that showed no response at this time were given a score of 1200 seconds.

In all animals, the first obvious abnormal response was a pronounced, highly dramatic myoclonic jerk. Characteristically, the animals would forcefully retract their head, extend their forepaws, and rapidly tense their body musculature such that a loud noise was generated. The movement only lasted a fraction of a second, and the animal would appear to immediately recover and continue moving in its cage.

All animals that received kainate lesions had a myoclonic response from 47-260 seconds after injection. One control animal

evidenced no response to the metrazol, one emitted a myoclonic jerk at 17.9 minutes, and the rest emitted responses between 36 and 700 seconds post-injection. Table 8 shows the response by the 2 groups on this measure. It indicates that the latency to the first ictal response was significantly shorter for the lesioned rats.

The latency to the first grand mal seizure was recorded by timing when the rats fell down with a loss of consciousness and tonic-clonic movements. Most often, this occurred immediately following a several second period of tonic, or tonic clonic, movements.

TABLE 8: FIRST ICTAL RESPONSE TO METRAZOL

	MEAN	S.D.
LESIONED	127.75	76.5
CONTROL	467.50	476.2

t=1.99; d.f.=14

P<.05

All lesioned rats experienced a grand mal seizure from 52-367 seconds. One control rat did not seize during the 20 minutes of obervation; a second control did not seize until 19.3 minutes after injection. The remaining control rats seized between 38-958 seconds. Table 9 shows that lesioned animals experienced a grand mal seizure in a

significantly shorter time than controls ($p<.05$).

TABLE 9: LATENCY TO THE FIRST GRAND MAL SEIZURE

	MEAN	S.D.
KAL	179.5	106.5
CONTROL	551.0	491.0

$t=2.09$; d.f.=14

$p<.05$

(f) HISTOLOGICAL EXAMINATION OF PATHOLOGY FOLLOWING KAINIC ACID LESIONS

Four animals with kainic acid lesions and three controls were sacrificed at the end of the pentylenetetrazol challenge, and were perfused first with phosphate buffered saline (PBS), then with a 30% solution of formalin/PBS (Note: the remaining animals were allowed to survive for an extended period of time to assess their weight changes over a three month period, and thus were not included with the histology for this experiment). Thirty micron coronal slices were cut on a freezing microtome, and every fifth section was mounted on a slide. Slides were stained with a 0.1% solution of cresyl violet, dehydrated with alcohol, and mounted in permount after treatment with xylene. Cell

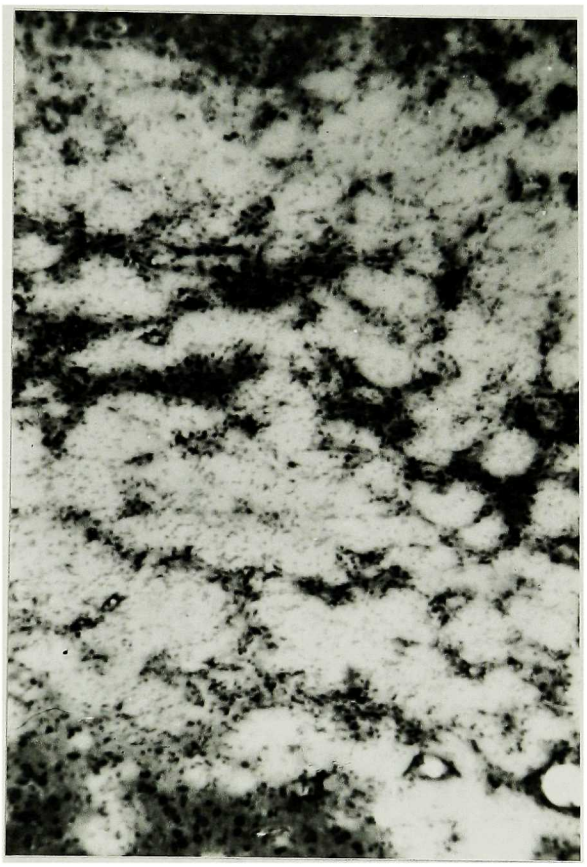
counts were obtained from seven brain regions, defined according to the atlas of Konig and Klippel (1967). These regions included the anterior striatum (8920u), caudal striatum (7890u), and striatum midway between these 2 regions (8280u), pyriform cortex (8280u), amygdala (7020u), hippocampus (3930u), and VMH (4230u). Neurons were counted in five high power (1000x) fields per brain area, averaged, and compared accross groups via the use of independant t-tests.

The anterior striatal regions were significantly depleted of neurons in comparison to controls, as shown in Photo One (lesioned) and Photo Two (control). The most caudal striatal area was less populated than controls, but the groups were not statistically different. The results from the cell counts are presented below.

A prominent gliosis (i.e. increased number of astrocytes, oligodendricytes, and microglial cells) was noted throughout the striatum in the lesioned only group. The number of microglial cells and astrocytes were pronounced. In addition, a marked ventricular dilatation was noted throughout the lateral ventricles in 3 of the 4 lesioned brains.

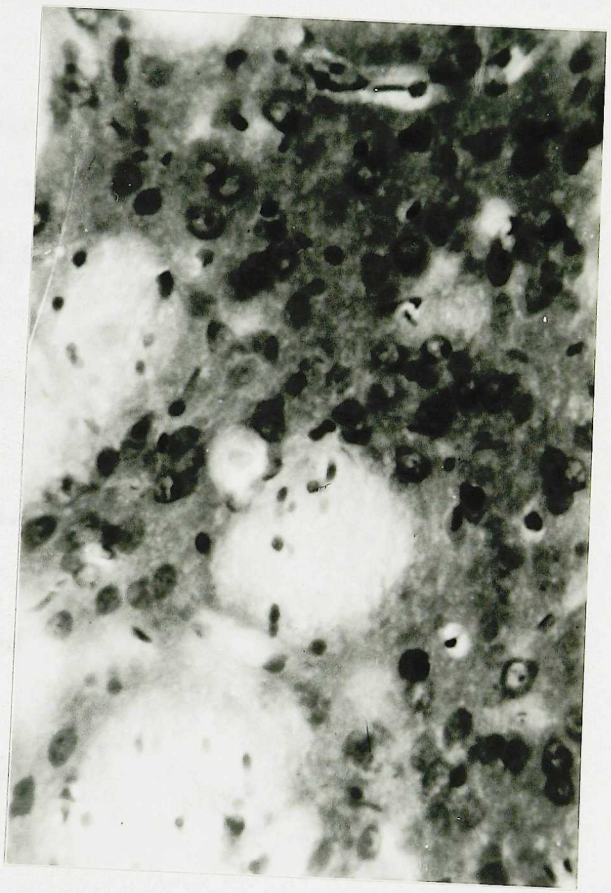
Although the cell counts of hippocampal pyramidal neurons in regions CA3-CA4 were not statistically decreased in animals with lesions, nonetheless two lesioned animals had unilateral destruction of CA3a that were discernible under the light microscope.

PHOTO ONE



Denervated region of anterior striatum with previous injection of kainic acid. Fibers of passage crowd together, due to death of neurons (300x; cresyl violet stain).

PHOTO TWO



High power (500x) magnification of middle region of previous photo, showing a prominent gliosis, but relatively few surviving neurons (cresyl violet stain).

CELL COUNTS

	LESIONED		CONTROL		T (5 df)	P
	X	SD	X	SD		
striatum						
8920	7.6	6.9	30.1	11.6	3.21	<.025
8280	7.7	9.8	31.1	9.6	3.11	<.025
7890	13.0	13.1	26.1	4.4	1.63	ns
pyriform						
8280	76.3	10.7	72.7	2.0	0.30	ns
amygdala						
7020	14.75	5.1	15.0	5.6	0.06	ns
hippocampus						
3930	24.9	6.6	32.1	6.0	1.46	ns
VMH						
4230	66.6	12.27	65.9	7.0	0.09	ns

In summary, the kainic acid lesions caused marked neuronal loss in the anterior striatum of the lesioned rats, as well as other pathological changes. Additionally, some distant lesions of CA3a of the hippocampus were noted. These findings replicated reports by others of similar histopathological changes following kainic acid lesions of the striatum (Coyle et al., 1977; Coyle, 1983; Divac et al., 1978; Dunnett & Iversen, 1981).

(vi) DISCUSSION

The findings in this experiment generally replicate and extend previous work reported by others. The hyperactivity in response to amphetmine, decreased T-maze performance, shortened latency to the first ictal resonse/ grand mal after injection with pentylenetetrazol, and temporary weight loss found in the lesioned animals have all been reported previously, as will be discussed below.

(a) SPONTANEOUS LOCOMOTOR ACTIVITY

Spontaneous locomotor activity was included as a behavioral measure in this experiment in an attempt to replicate previous work done on male rats with kainic acid lesions of the striatum. A number of authors (Sanberg, Pisa, & Fibiger, 1978; Dunnett & Iversen, 1981; Mason et al., 1978a; 1978b) have reported that for up to 3 weeks after kainic acid lesions of the striatum, there is no difference in general daytime locomotor activity or rearing behavior. This experiment replicates those earlier findings. On each of the ten spontaneous locomotor behaviors measured, there were no significant differences on either the between subjects or lesion x time in monitor interaction effects.

The significant time in monitor repeated measures effect found on each measure indicates that, over the 2 hours they spent in the field, the rats moved less as the time they spent in the monitor increased. This effect is of little experimental interest, as there was no difference between groups, and as these results are predictable. They indicate that the animals become accustomed to the monitor, whether due

to habituation to the novelty of the field, muscular fatigue, sleepiness due to interruption of their sleep cycle, or other reasons.

(b) AMPHETAMINE-INDUCED ANIMAL ACTIVITY

The purpose of assessing locomotor activity after amphetamine administration was to replicate the findings of other investigators regarding the effects of amphetamine in rats with kainic acid lesions of the striatum. Previously, Sanberg et al. (1979b), Fibiger (1978), and Mason et al. (1978a; 1978b) reported that administration of 1 mg/kg of d-amphetamine causes a significant increase in activity of kainic acid lesioned rats in comparison to control rats. It is important to note that the equipment they used to measure these effects was an earlier generation of the apparatus used in this experiment. Their activity monitors consisted of either three or six photocell beams set in the horizontal axis only. It assessed behavior by counting the number of beams broken by the animals during the time they were in the field. Thus their measures were most equivalent to this experiment's measure of horizontal activity and total distance travelled. Their apparatus had no ability to assess vertical activity, time spent moving, or stereotypy, and thus there was no equivalent measure to (in this experiment) number of movements, time moving, rest time, vertical activity, vertical time, vertical rears, stereotypical movement time, or number of stereotypical movements.

This experiment replicated and extended the reports of these earlier authors. There was a significant increase in horizontal activity by the lesioned rats given amphetamine compared to controls. It extended the horizontal activity findings by demonstrating that the

lesions led the rats to travel further in the horizontal plane than the controls, and caused the lesioned rats to move in fewer (in number) but longer (in time) discrete bouts of horizontal activity.

Additionally, this experiment found the effect of the amphetamine to be limited only to the horizontal axis. Unlike the horizontal movements, there was no corresponding increase in vertical movements after amphetamaine injection. Indeed, there was a nonsignificant trend for the lesioned animals to be relatively less active than controls in the vertical plane.

Although several authors (Fibiger, 1978; Mason et al., 1978a; 1978b) have reported that stereotypical response (as measured by rating scales of biting, licking, grooming, etc.) increases in rats with striatal kainic acid lesions compared to controls in doses of amphetamine from 5 mg/kg--10 mg/kg, this effect has not been found in lower doses (Sanberg, personal communication). This experiment replicated this finding, as the lesioned rats showed no significant difference from controls on the measure of stereotypical movements.

Fibiger (1978) explained his findings of increased response to amphetamine in the lesioned rats by discussing the relationship between the dorsal striatum, the substantia nigra, and the nucleus accumbens, all areas that utilize dopamine as a putative transmitter. He postulated that the normal circuitry of the brain was for the dorsal striatum to send inhibitory projections to the substantia nigra, pars compacta (SNC), which in turn sends excitatory projections to the nucleaus accumbens, which then modulates locomotor behavior. He cited unpublished work that found that rats with kainic acid lesions of the striatum had a loss of the usual inhibition of single units in the SNC in response to amphetamine administration. He concluded that one of the

effects of amphetamine in the normal rat was to act in the dorsal striatum to activate a striatonigral negative feedback loop and inhibit cells in the SNC. Since the amount of dopamine released into the postsynaptic cleft in the nucleus accumbens is a combined function of amphetamine and the firing rate of SNC neurons, then the stimulation of the postsynaptic receptors in the accumbens will be the balance of these two opposing actions (i.e. directly stimulating SNC cells will release dopamine, while indirectly inhibiting them via excitation of the striatal inhibitory input). Thus removing the negative feedback action of amphetamine by lesioning the striatum leads to increased dopamine production by the SNC cells minus the inhibitory input, in turn leading to increased excitation of the nucleus accumbens and thus hyperactivity. This hypothesis explains why amphetamine has, and apomorphine (a direct receptor agonist) has not, an effect in changing the activity in rats with kainic acid lesions of the striatum. Apomorphine binds directly to the nucleus accumbens, unaffected by presynaptic events in the SNC. Since there is no change in receptor sensitivity in the nucleus accumbens, there is no change in the relative hyperactivity due to the apomorphine.

Finally, the results from the amphetamine challenge contrast with the measures of spontaneous locomotion, where no difference between groups was found. Taken together, these results suggest that tonically, the striatum has little or no effect on modulating rat movements. It is only in the setting of activation of the striatal region via administration of dopamine that a disinhibition of locomotor activity occurs, and then only in the horizontal plane. Thus it can be concluded that the striatal region of the rat acts as an inhibitor of horizontal movement, but only when the system is activated. Under spontaneous

conditions, its effect on movement is undetectable.

(c) BODY WEIGHT CHANGES

It has previously been reported that, after kainic acid lesions of the dorsal striatum, lesioned animals show a temporary aphagia, adipsia, and body weight reduction that lasts from 1-5 days postoperatively (Pettibone, Kaufman, Scally, Meyer, Ulus, & Wyatt, 1978; Sanberg & Fibiger, 1979; Sanberg, Lehmann, & Fibger, 1978; Sanberg et al., 1979). This experiment replicated the body weight finding, with lesioned rats dropping an average of 24.87 grams over the first 24 hours after surgery (while controls gained 2.6 grams), and regaining that weight over the next 5 days.

Sanberg and Fibiger (1979) additionally reported that, while the rate of weight gain in rats with kainic acid lesions returned to a level comparable with that of the control group, the initial loss was not made up. Their lesioned rats maintained a consistent and significantly lower weight compared to controls. This experiment did not replicate that finding. The weight loss in the experimental groups was significant only for the first day after surgery. However, the same trend was found in this experiment as in Sanberg and Fibiger's. Beginning at day 6 postsurgery, lesioned rats plateaued in their rate of weight gain compared to presurgery levels, leaving them 3-6 grams lighter than the control group. Thus in this experiment, there was a consistent loss of weight in the lesioned animals which did not reach significance.

Two explantations may account for the differences between this experiment and Sanberg and Fibiger's. First, Sanberg's experiment used lesioned rats that, as a group, were approximately 20 grams lighter than

controls presurgery. While not enough to be statistically different, when the additional weight loss caused by the lesioning was added on, it increased the likelihood of their finding between group differences. As only raw weights were used in their computations, no compensation of this difference in weights was made, leading their results to being biased in the significant direction. This experiment, however, was initially biased in the opposite direction from that of Sanberg and Fibiger, with the lesioned animals weighing approximately 20 grams more than controls presurgery. Thus the presurgery weight difference, and the method of doing the statistical analysis, may partially explain this discrepancy.

In summary, this measure replicated findings of a temporary weight loss following kainic acid lesions of the striatum. Additionally, while not replicating the quantitated differences found by Sanberg and Fibiger, qualitatively the same trend of weight decline was found.

(d) T-MAZE RESULTS

Previous reports that kainic acid lesions of the striatum lead to large and persistent deficits in rewarded alternation up to 3 weeks following surgery were replicated in this experiment. Pisa et al. (1979) found that all of their kainic acid treated animals failed to learn their food reinforced spatial alternation task. Divac et al. (1978), in an experiment that closely paralleled the methodology in this experiment, found that on 60 trials in a rewarded alternation task, lesioned animals performed at about the chance level, significantly worse than controls. Each of these studies employed postoperative

periods of 3 weeks or less.

This experiment replicated those findings. A persistant and significant deficit in performance was noted throughout the 200 trials of postsurgery maze running. The deficit is not due to a simple forgetting of the presurgery training by the lesioned rats (although this may have contributed to the effect). On the first day of presurgery training, lesioned rats alternated 60-75% of the time. If the rats had only "forgotton" the task, they would have alternated at the same level post surgically as on the first day of training presurgery. In fact, on the average they alternated less than 60% of the time for the first six postsurgery sessions. Thus the lesioned rats had less of a capability to perform on this measure. The lesioned rats were, however, capable of improving their performance on the maze. Starting with the second postsurgical session, the lesioned rats increased their performance on the maze at a rate that equalled or surpassed that of the controls. Thus the lesioned animals were able to relearn the paradigm at a similar rate as controls; it was their overall capability to perform this task that was decreased.

One contributing factor to the decreased performance by the lesioned rats was their tendency to alternate to the same side in the maze. Whereas the control rat would often enter the same arm twice and make a mistake, it would rarely enter the same side of the maze on three consecutive visits, having "learned" that the food was not there. The lesioned rats, however, frequently entered the same arm on three or more consecutive trials. The cause of this may be a simple short term memory deficit, preventing the rats from remembering which arm they entered. This would predict that the rats would perform at about a chance level, which in fact occurred during the first 5 trials. However, as the

lesioned rats get better on the task over time, it appears that they are remembering the task from day to day. Thus the precise cause of this increased perseveration is unclear, and may include factors as diverse as memory deficits, sensory inattention, dominance of side preferance, motoric dysfunctioning, etc.

(e) PENTYLENETETRAZOL RESULTS

Pisa, Sanberg, Corcoran, & Fibiger (1980) previously found that, 45 days after surgery, rats with kainic acid lesions of the striatum responded differently to the convulsant pentylenetetrazol than did controls. Specifically, lesioned rats showed significantly decreased latencies to the first ictal response, and significantly decreased latencies to the first generalized convulsion. This effect was found 45 days after surgery.

This experiment replicated the finding of Pisa, Sanberg, Corcoran, & Fibiger (1980). At 25 days post kainic acid surgery, lesioned rats were found to exhibit pentylenetetrazol induced myoclonic motions significantly quicker than controls. Additionally, they experienced grand mal seizures after a shorter amount of time post pentylenetetrazol injection, in comparison to controls. Thus on both the time to first ictal response, and time to first grand mal seizure, this experiment replicated the findings of Pisa's group.

(vii) GENERAL DISCUSSION

This experiment was designed to replicate previous work done on

the behavioral effects of kainic acid lesions of the striatum in male rats. It was intended to serve as further validation of a series of experiments done by Fibiger and Mason (and their associates) by replicating their findings in a different laboratory. Additionally, it allowed this laboratory to demonstrate its ability to successfully perform the kainic acid surgery and assess its behavioral consequences. All of these goals were accomplished. The summary table listed on the following page compares the findings from this experiment with those of other laboratories.

First, this experiment replicated the finding that kainic acid lesions of the striatum do not disrupt spontaneous locomotor activity (Dunnett & Iversen, 1981; Mason et al., 1978a; 1978b; Sanberg et al, 1979b). It extended the amphetamine findings by revealing that the hyperactivity is specific to movement in the horizontal plane. Movement in the vertical plane was nonsignificantly decreased compared to controls.

Secondly, the temporary weight loss others have reported in this model (Pettibone et al., 1978; Sanberg et al., 1979a; Sanberg & Fibiger, 1979) was also found in this experiment. Kainic acid lesioned rats dropped significantly in weight the first day postlesion, and then returned back to a near control level. The persistent 3-6 gram deficit in weight between control and lesioned change scores noted over the 10 days after lesioning, although not statistically significant, are in the same direction as the finding of Sanberg and Fibiger (1979). The quantitative differences between their results and this experiment are most probably a result of differing relative presurgery weights between controls and lesioned rats.

Thirdly, the lesioned rats showed severe and persistent deficits

in modulating many diverse forms of behavior. Furthermore, they suggest that the anterior medial striatum in rats is not involved in the regulation of spontaneous locomotion, but does lead to disturbances in locomotion under the "activated" state seen after amphetamine administration.

COMPARISON OF FINDINGS IN EXPERIMENT ONE WITH WORK DONE PREVIOUSLY

BEHAVIOR	AUTHORS	FINDINGS	THIS EXPERIMENT
T-MAZE	1) Pisa, Sanberg, & Fibiger, 1978	1) ↓ alternation; training started 10 days post kals	1) replicates finding of these experiments---training began at 16 days post kals
	2) Divac, Markowitsch, & Pritzel, 1978	2) ↓ alternation; training started 2 weeks post kals	
LOCOMOTOR ACTIVITY AFTER KALS			
a) spontaneous daytime activity			
	1) Dunnett & Iversen, 1981	1) no change after kals at 2 weeks	1) replicates finding of these experiments---no change in daytime activity at 2 weeks post kals
	2) Mason, Sanberg, and Fibiger, 1978(a); 1978(b)	2) no change after kals at 2 weeks	
	3) Sanberg, Pisa, and Fibiger, 1978	3) no change after kals at 2 weeks	
	4) Sanberg, Pisa, and Fibiger, 1979	4) no change after kals at 3 weeks	
b) amphetamine activity			
	1) Fibiger, 1978	1) kal animals hyperactive over hour after amphetamine injection	1) kal animals hyperactive in the horizontal, but not vertical, plane over hour after injection
	2) Mason, Sanberg, and Fibiger, 1978(a); 1978(b)	2) kal animals hyperactive over hour after amphetamine injection	
	3) Sanberg, Pisa, and Fibiger, 1979	3) kal animals hyperactive over hour after amphetamine injection	
BODY WEIGHT CHANGES AFTER KALS			
	1) Sanberg & Fibiger, 1979	1) animals initially adipsic and aphagic; suffer permanent weight loss	1) animals have a temporary weight loss, presumably due to temporary adipsia and aphagia; have permanent, nonsignificant weight loss
	2) Sanberg, Pisa, and Fibiger, 1979(a); 1979(b)	2) temporary adipsia and aphagia	
	3) Pettibone et al, 1978	3) temporary adipsia and aphagia	
	4) Divac et al, 1978	4) temporary adipsia and aphagia	
	5) Sanberg, 1979	5) temporary adipsia and aphagia	
SEIZURE ACTIVITY AFTER KALS			
	1) Pisa, Sanberg, Corcoran, and Fibiger, 1980	1) ↓ latency to first ictal response and first grand mal after metrazol injection	1) ↓ latency to first ictal and first grand mal after metrazol injection

EXPERIMENT TWO

EXPERIMENT TWO

(i) GENERAL OUTLINE OF EXPERIMENT II

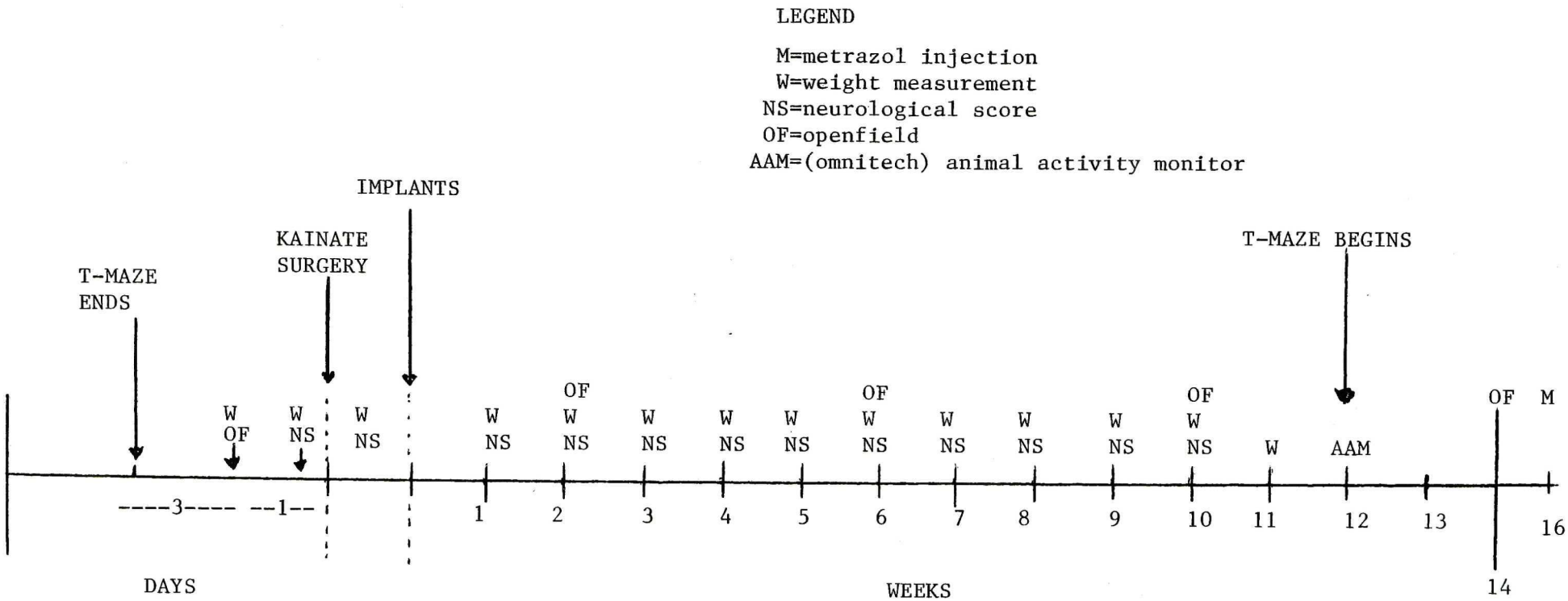
This experiment was designed to compare and contrast three groups of animals on seven different behavioral tasks. It had two main purposes, including 1) to assess the behavioral consequences of kainic acid lesions in female, as opposed to male, rats, and 2) to determine if fetal striatal transplants were able to remediate the behavioral deficits following the kainic acid lesions.

For reasons previously described, female Sprague-Dawley rats were used in this experiment. All behaviors were run in a room maintained at a constant temperature of 68 degrees Fahrenheit, the order of which is schematically outlined in Table 11.

After 3 days of gentling (5 minutes/day) to acclimate the rats to human touch, all animals were reduced to 85% of their ad lib body weight. Following this, rats were trained to criteria on a T-maze (i.e., alternating 85% or better on three consecutive days). This behavior was assessed because of its documented sensitivity to the kainic acid lesions being employed (Divac et al., 1978; Pisa et al., 1978). After completion of this training, animals were given 3 days of ad lib feeding to return to normal weight, and then were assessed in a traditional open field. Specifically, spontaneous locomotor activity (i.e. squares crossed and number of rears) was measured for the first 5 minutes in the field, and, 55 minutes later, again for 5 minutes. This gave a measure of locomotor activity both before and after experience in the field. Immediately after the second count was obtained, animals

TABLE 11

EXPERIMENT TWO: SCHEDULE OF BEHAVIORAL TESTING



were injected with d-amphetamine sulfate (1.0 mg/kg/2cc water), and squares crossed and number of rears were counted at minutes 5-10, 20-25, and 55-60 postinjection (Note: the Omnitech apparatus used in experiment one was not available for these animals, necessitating the use of the open field in its place). Previous work (Fibiger, 1978) had shown that these times allowed for the assessment of early, peak, and waning effects of the amphetamine on the locomotor behaviors. Twenty four hours later, when the effects of the amphetamine had passed, the animals were weighed, and a prelesion neurological exam was obtained. This exam was patterned after previous work (Dunnett, Bjorklund, Stenevi, & Iversen, 1981), and was intended to provide information on a number of different neurological measures, including olfaction, orientation (on a rostral to caudal gradient) to blunt and sharp touch, and strength.

Rats were then randomly assigned to one of the three groups, based on the number of trials taken to reach criteria on the T-maze. Groups included a control, lesioned only, and lesioned and transplanted group. Kainic acid lesions (0.8 ugms/0.4 ul PBS/4.5 minutes/side, bilaterally) were then made in the dorsal medial striatum in six to seven surviving animals per group.

Three days following surgery, a postlesion neurological score (see methods), and the animal's weight, were obtained. For the following 10 weeks, weekly measures on these two tasks were taken in order to monitor the recovery of the animals on these measures throughout the course of the experiment. Ten weeks was chosen because it allowed for a sufficient amount of time to pass for the implanted tissue to mature and send efferent projections to its natural target tissues (Labbe et al., 1983; Bjorklund, Dunnett, Stenevi, Lewis, & Iversen, 1980; Bjorklund & Stenevi, 1977a; 1977b; Dunnett, Schmidt,

Bjorklund, Stenevi, & Iversen, 1981).

Seven days after surgery, the lesion and implanted group received implants of day 18 fetal rat striatum into the lesioned striatal area. This time span was chosen because (1) the kainic acid remains active for up to 5 days following its injection (Coyle, McGeer, McGeer, & Schwarcz, 1978; Coyle, Molliver, & Kuhar, 1978; McGeer & McGeer, 1978), thus limiting how quickly the implants can be placed in the striatum, and (2) previous work done under identical conditions (Deckel, Robinson, Coyle, and Sanberg, 1983) revealed that grafts transplanted into kainic acid lesioned striatum seven days postlesionsurvived and behaviorally influenced the host rat. Day 18 tissue was chosen because of its ability to increase in volume slightly, but not excessively, after implantation (Hallas et al, 1972; Das, Altman, & Das, 1972). All other animals received sham implants at that time.

At weeks 2, 6, 10, and 14 following implantation, all animals were tested on the open field measure as previously described. This time course had been chosen to allow for periodic assessment of recovery of functions in the lesioned animals. These measures were intended to substitute for the Omnitech apparatus, which was not available during most of the time this experiment was underway. However, 2 hours per rat was available in the activity monitors at the end of the experiment, and thus at 12 weeks postimplantation, all animals were placed the animal activity measure (Omnitech, Model DCM-8, Columbus, Ohio) to assess spontaneous activity. The measurements were identical to those obtained on spontaneous locomotion in experiment one, and included bouts of movement, time spent moving, bouts of rearing, time spent rearing, vertical activity, bouts of horizontal activity, total distance traveled, time spent resting, bouts of stereotyped movements, and time

spent performing stereotyped movements every 10 minutes during the course of a 2 hour testing period. This measure was done at 12 weeks because it allowed for sufficient time to pass for the implants to mature and reconnect with target tissues.

Immediately following completion of the analysis of spontaneous activity in the animal activity measure, the rats were food deprived to 85% of their ad lib body weight over the course of one week. Subsequently, they were rerun in the rewarded alternation task for 10 days (200 trials), a period of time previously shown to allow for assessment of differences betwen lesioned and control animals (Divac et al., 1978; Pisa et al., 1978). Upon completion of this task, animals were given at least 3 days to return back to normal weight, so as to be physically capable of surviving the metrazol challenge they received prior to sacrifice.

The last behavioral measure done was assessment of convulsant activity in response to injection of metrazol (70 mg/kg/1 cc water, s.c.). This measure was performed at 4 months, and was done last because pilot testing revealed that not all animals survived. Latency to the first ictal seizure response, latency to the first grand mal convulsion, and duration of the first grand mal seizure was assessed exactly as done in the experiment one. Previous work (and the results from experiment one) revealed these two measures to be sensitive to kainic acid lesions (Pisa, Sanberg, Corcoran, & Fibiger, 1980).

The behavioral measures were administered in a way designed to keep the influence of one behavior over the next at a minimum. Thus, no measure was administered during, or for the few days after, the T-maze training, when animals were in a food deprived state. Similarly, no measures were given for the 24 hours after amphetamine administration.

The order of presurgery measures (i.e., T-maze, amphetamine challenge on the openfield, and neurological exam) was decided on for two reasons. First, not all food deprived rats eat pellets in the maze. Thus screening them first on this task allowed for identification of these animals prior to the investing of much time and effort in them. Secondly, the most physically taxing measures were done initially to give the rats a greater period of time to recover prior to their undergoing the surgery. Thirdly, because of the strain the food deprivation (for the T-maze) placed on the animals, it was done first so as to allow the rats to have maximal amounts of time to recover prior to surgery. For these reasons, counterbalancing of groups was not carried out, but rather was controlled for across groups by identical presentation of presurgery behaviors.

Following the completion of the behavioral measures, the animals were perfused, the brains removed, and histology was done.

(ii) METHODS

(a) SUBJECTS

Adult female Sprague-Dawley rats of approximately 4 months age, weighing between 250-300 grams at the start of the experiment, were used. These animals were chosen in order to allow this experiment to assess the effects of sex and strain on the behaviors previously reported to be affected in male rats with kainic acid lesions of the striatum.

Seven animal per cell (i.e., animals that: 1) ran the T-maze, 2) survived the kainic acid/sham surgery, and 3) survived the

transplantation/sham transplantation) began the experiment. Because of a failure of a watering device, one transplanted animal died midway through the experiment, giving a total of 20 animals (7 controls, 7 lesioned only, and 6 lesioned and transplanted) in the experiment. The rats were maintained on a 12 hour light/dark cycle, and maintained identically to the rats in experiment one, except that they were housed three per cage (due to limited female housing space) except when being food deprived.

(b) SURGERY

The surgical procedure used in this experiment was identical in every manner to that described in experiment one.

(c) IMPLANTATION

Seven days after the kainic acid lesions, day 18 fetal striatum was implanted into the lesioned area. The technique of Das et al. (1979) was followed. A transplantation syringe was constructed out of a 0.25 ml glass tuberculin syringe and a 25 gauge needle, over which the transplantation glass needle was fitted. The transplantation needle consisted of fine capillary tubing, with an outer diameter of 0.80 mm, an inner diameter of 0.60 mm, and a length of 3.0 cm. The capillary glass tubing was polished to a sharp end in a sharpening stone, flamed to reduce the ragged edges, and sealed with epoxy to the 25 gauge needle.

Adult female rats, after being left overnight with an adult stud rat, had vaginal smears obtained by aspiration of the vaginal contents into a small plastic syringe, and those showing smears under the light

microscope that contained sperm were taken as embryo donors. At day 18 postconception, the females were anesthesized with 0.30 cc/100 gms of chloropent, and a laparotomy exposing the uteri was done. Viable embryos were removed one at a time by cutting open the uterine wall and amniotic sac. The embryonic brains from the exposed fetus were then removed by peeling back the cranium and pinching out the fetal brain. The fetal brain was then placed in lactated Ringers solution, and the left or right striatum was removed under the dissecting microscope. To remove the striatum, first the posterior two-thirds of the brain was removed and discarded. Then the cortex from the remaining anterior portion was cut away until the lateral ventricle was reached. The outgrowth of fetal neural tissue inferior to the ventricle, and on its lateral surface, was taken as donor striatal tissue. First, left fetal striatum was implanted into the left adult striatum, then the right side was done.

Two cubic millimeters of fetal striatum was taken into the transplantation needle, and stereotaxically injected over the course of several seconds into the recipient rat. The coordinates for the transplantation, from bregma, were A 1.5 mm, L 2.2 mm, and H 5.3 mm. Pilot work showed this to deposit the tissue into the lesioned adult striatum.

(iii) BEHAVIORAL TRAINING

(a) T-MAZE TRAINING

Pre and post training was done on this measure in a manner identical to that described for experiment one, with the exception that

the postsurgery trials were run at 12 weeks after implantation. Twelve weeks was chosen because it was sufficient time to allow the implants to fully mature and develop. This maximized the chance that the implants could mediate the behavioral deficits that resulted from the kainic acid lesions of the striatum.

(b) OPEN FIELD

In order to assess performance on this measure over time after lesioning, each animal was given five, 2 hour sessions in the open field. Two hours was chosen as the time span for this measure based on previous work (Mason et al., 1978a; 1978b; Mason & Fibiger, 1979; Sanberg et al., 1979b). Animals were tested preoperatively, and at 2 weeks, 6 weeks, 10 weeks, and 14 weeks postimplantation. These periods were chosen as they allowed a monthly monitoring of recovery from the lesions. As the purpose of this measure was to assess changes in locomotion, two behavioral measures, including squares crossed and rears, were obtained for five different times in each session. These two measures were chosen because they represent easily quantifiable measures of locomotion in each of the two common planes of movement without requiring any elaborate equipement, and because the Omnitech equipment was available only for a limited amount of time at the end of the experiment.

(1) APPARATUS FOR OPEN FIELD

The open field was constructed out of wood and plexiglass placed on the floor, with wooden walls 30 inches wide, 36 inches long, and 18

inches high. The floor was constructed out of plexiglass, and was marked off by squares 6 x 6 inches wide.

(2) METHODS FOR OPEN FIELD

Spontaneous activity was assessed early during the rats light cycle. This was done by counting the number of times the rat's front paws crossed into a new square (squares crossed) or by counting the number of times the two front paws left the surface of the field in a rear (rears). This was done for the first 5 minutes the rats were placed in the field in order to get a measure of spontaneous locomotion, and then again for 5 minutes 55 minutes later to get a measure of activity prior to amphetamine injections. Following this, and after a total of one hour in the open field, the rats were given an i.p. injection of d-amphetamine sulfate, 1.0 mg/kg, dissolved in 2.0 mls of sterile water. The same measures of locomotor activity, including squares crossed and rears, were then measured for three 5 minute periods postinjection. These measurements were made at minutes 5-10, 20-25, and 55-60 postinjection.

These times were chosen for several reasons. Minutes 5-10 were picked to serve as a measure of early effects of the drug on locomotor ability. Pilot testing revealed that minutes 0-5 postinjection frequently resulted in severe dystonic movements in the animals. These dystonic movements interfered with locomotion, and were mostly gone by 5 minutes postinjection. Minutes 5-10 postinjection served two purposes, including (1) that the period of severe dystonia was avoided, and (2) these dystonic movements were able to be observed and quantified.

Minutes 20-25 were picked as a time when the effect of

d-amphetamine in open field activity had peaked. Previous studies (Sanberg et al., 1979b; Fibiger, 1978) have revealed that this peak activity occured between 20-30 minutes postinjection.

Finally, the third postinjection open field measure was obtained at minutes 55-60. The previous studies just cited reported that the hyperactivity at that time, although waning, still differentiated between control and kainic acid lesioned rats. Thus the measure allowed for assessment of later effects of the drug on open field activity.

(c) NEUROLOGICAL TESTING

The neurological test was based on the rat neurological test batteries of Dunnett, Bjorklund, Stenevi, and Iversen (1981). Several sections of the battery not sensitive to the striatal lesions were eliminated following pilot training, and the final battery included measures of orientation and limb use. It was administered in a stereotypical manner such that the most aversive measures were not given until the end of the exam so that they did not interfere with the more subtle tests. As described in more detail in the following section, the order of the testing was: 1) a measure of muscle tone of the distal extremities, 2) vibrassae and olfaction orientation, 3) response to blunt touch, 4) response to sharp touch, and 5) limb strength.

In each of these tests the stimulus was applied first to the left side of the body and then to the right. The orientation of the animal was rated, on a 3 point scale, as absent (0), weak (1), or strong (2). In order to score a 2, the head of the animal had to turn towards the stimulus, and one of the following also had to occur; 1) the movement had to be very forceful, 2) the body of the animal needed to turn toward

the stimuli, or 3) the animal moved the affected limb away from the aversive stimulus. In order to score a 1,the animal needed to make only a weak head movement, or only turn its body, or only move the affected limb away from the aversive stimulus. A score of 0 indicated that none of the above had occurred.

(1) NEUROLOGICAL TEST OF ORIENTATION

The following measures were used:

(a) whisker touch---the vibrassae were lightly touched using a plastic probe from behind or below the rat to reduce visual cues,

(b) snout touch---the probe was lightly brushed against the snout of the animal, approaching from the side,

(c) olfaction---a fine paint brush was soaked in Lysol solution and was brought slowly towards the nose of the animal from either side or below,

(d) blunt touch---a blunt plastic probe was applied to six different sites on the lateral surface of the body, including at the level of the shoulder girdle, middle of the body, and hip girdle,

(e) sharp touch---a firm pin prick was applied to eight different sites, including the lateral aspects of the forepaws, shoulder girdle, middle of the body, and hip girdle. The animal was given 5 seconds of stimulation, and the most intense response given by the animal during that time period was taken as the score.

(2) NEUROLOGICAL TEST OF LIMB USE

(a) muscle tone---each of the animals' four limbs were manually

manipulated in order to assess the average resistance exerted during passive flexion. A score of 2 was given for normal resistance, 1 for some rigidity of the limb, and 0 for extreme rigidity.

(b) limb strength---the animals were alternatively suspended by their left or right paw in the air. The time it took for the animal to grasp with all four limbs the glove that was holding the paw were recorded. Based on Dunnett, Bjorklund, Stenevi, and Iversen's work (1981), a score of less than 3 seconds was worth 2 points, from 3-7 seconds was given 1 point, and greater than 7 seconds was given 0 points.

(d) EVALUATION OF SPONTANEOUSLY EMITTED LOCOMOTOR ACTIVITY

Twelve weeks after implantation/sham implantation, animals were placed in the animal activity monitors, and spontaneous activity was assessed in exactly the same manner as described in experiment one. Twelve weeks was decided on for two reasons: (1) at the start of the experiment, there was very limited access to the monitors, with only one 2 hour slot per animal available for this experiment, and (2) twelve weeks is a sufficient amount of time to allow the implants to fully mature and develop. Thus it was decided to use this time span as it would allow for assessment of the behavioral integration of the grafts at a time that would maximize the chances of detecting differences between groups.

(e) METRAZOL-INDUCED CONVULSANT ACTIVITY

This measure was performed after the completion of all other

measures, as pilot testing revealed this task to frequently be fatal for lesioned animals. Thus, at 4 months, convulsions were induced in animals, and latency to the first ictal response and grand mal seizure were measured exactly as described in the METHODS section of experiment one.

(iv) HISTOLOGICAL EXAMINATION OF KAINIC ACID/TRANSPLANTATION EFFECTS

After kainic acid lesions of the dorsal striatum, cell damage has been reported in various other regions of the brain, presumably because of the distant excitotoxic effects of the rapidly discharging striatal cells. Other areas noted to be lesioned include the hippocampus, pyriform cortex, cerebellum, and amygdala (Coyle, Mollier, & Kuhar, 1978; Olney & deGubareff, 1978; Pisa, Sanberg, & Fibiger, 1980; Wuerthele et al., 1978). To evaluate the extent of striatal and extrastriatal damage from the kainic acid, and to assess statistically the extent to which the transplants grew, cell counts were done on six regions of the brain. These regions included: striatum rostrally (8920u), caudally (7890u), and centrally to these two sites (8280u), pyriform cortex (8280u), amygdala (7020u), and dorsal hippocampus (regio inferior, 3430u). Five cell fields per area were counted under high magnification (1000x), averaged, and tallied. An ANOVA was done on the cell counts from each of these brain regions to then determine if any between group differences existed.

The tissue preparation and basic staining techniques used were adopted from the methods of Clark (1978). Animals were anesthesized and perfused transcardially with phosphate buffered saline and 10% buffered

formalin. The brains were removed and stored for at least 3 days in the buffered 10% formalin, then in a 10% formalin/sucrose solution for at least another 3 days. Brains for cresyl violet histology were then processed exactly as described in experiment one.

In addition to the cresyl violet histology, tyrosine hydroxylase (TH) immunocytochemistry was done in the neuropathology laboratories of Donald Price at Johns Hopkins, according to a protocal developed by that lab. This was done in an attempt to assess if the transplants were able to direct dopaminergic fibers (presumably from the substantia nigra) into the transplant itself. TH was used as it is the rate limiting step for catecholamine synthesis, and serves as a marker for dopaminergic terminals in the striatum.

Specifically, animals were anesthesized with ketamine, followed by sodium pentobarabital, 0.30 cc/100 grams. Animals were perfused transcardially with 300 cc of phosphate buffered saline (PBS; phosphate buffer with 0.85% NaCl, ph 7.6), followed by 300 cc fixative containing 4.0% paraformaldehyde and 0.1% glutaraldehyde in phospate buffer (ph 7.6).

Sections through the striatum were cut in a cryostat at 14-100um thickness into cold tris buffered saline (TBS; trizma base and tris HCL, ph 7.6). All sections were pre-washed in 0.2% TritonX-100 in TBS for 15 minutes at room temperature in order to facilitate the penetration of subsequent antibodies into the tissues. Following this detergent treatment, sections were washed three times for 5 minutes each in TBS. In order to block nonspecific binding of the primary antisera, all sections were incubated in 3.0% normal goat serum (NGS) (Dako, Accurate Chemical Co.), which was prepared in TBS, for 30-60 minutes at room temperature. Sections were then placed in the anti-TH antibody at a

dilution of 1:1000, which was prepared in TBS with 1% NGS and incubated at 4 C for 16-24 hours. Following this incubation period in the primary antiserum, tissue sections were washed three times for 5 minutes in TBS at room temperature and then transfered to 5 ml polystyrene tubes that contained the binding antibody, goat anti-rabbit immunoglobulin (Cappel Labs.), which was diluted 1:50 with TBS and 1.0% NGS and incubated for 30 minutes at room temperature. Sections were removed from the binding antibody and washed three times for 5 minutes in TBS after which time they were transferred to a rabbit peroxidase-anti-peroxidase (rPAP) complex at a dilution of 1:100 that was made in TBS and 1.0% NGS and incubated for 30 minutes at room temperature. All sections were then washed three times for 5 minutes in TBS and reacted with diaminobenzidine (DAB) (0.44 mg DAB/350 ul 0.5 M tris buffer; ph 7.6, to which 0.04 ul of 30% H2O2 has been added) for 5-15 minutes. All sections were then washed thoroughly in TBS, mounted out of sodium acetate buffer (ph 6.0) onto subbed slides, rapidly dehydrated through a graded series of alcohols and xylenes and coverslipped with Permount. Selected sections were also stained with cresyl violet in order to facilitate the visualization of neuronal cytology and morphology. All sections were examined under light microscopy.

Immunocytochemical control sections were prepared as above with the exception that these sections were incubated in NGS instead of the TH antiserum at a dilution of 1:1000, which was made in TBS with 1.0% NGS added.

(v) RESULTS

SUMMARY OF ANALYSIS STRATEGY

For each of the 10 different types of locomotor behaviors, a two factor split plot factorial ANOVA with 12 repeated measures was performed with an unweighted means solution, according to the method of Kirk (1968). The unweighted means solution was the most appropriate analysis, as the transplanted group had one less animal than the other two groups due to an unexpected animal death (not related to experimental manipulation).

If the overall F test was significant either for the between group or interaction analysis, a priori contrasts (notated throughout the text as a "t" statistic) were done between the implanted group and the lesioned only group, and between the implanted and control group (Kirk, 1968). Additionally, a post hoc Tukey ratio (notated in the text as a "q" value) was done between the lesioned only and control group (Kirk, 1968). A priori contrasts were used to test the hypothesis generated prior to the initiation of the experimental work, i.e., that the implanted group would appear similar to sham lesioned controls, but different from lesioned only animals.

This same analysis strategy was performed on all behavioral measures that required a repeated measures analysis, including the T-maze, neurological exam, weight changes, food and water consumption, and open field measures. For most other analyses, including the cell counts between different brain regions, and the convulsive responses to metrazol, a one-way AVOVA was done to compare the groups, and individual comparisons were done between groups as described above when significance was detected. Finally, correlated t-tests were used to analyze the results on the T-maze perseverations. A rationale and

further explanation of this procedure is given in detail below.

(a) SPONTANEOUS ANIMAL ACTIVITY

Twelve weeks after implantation/sham implantation, all animals were placed in the animal activity monitor for a 2 hour period. For each animal, 10 different types of locomotor behavior were counted and recorded over 12 sets of 10 minute time intervals.

(1) MOVEMENT TIME

This is a measure of the amount of time the animal moved with sufficient speed to break at least one photocell beam per second in the activity monitor. The analysis of variance summary is shown in Table 10. While the between subjects effect was nonsignificant, the repeated measures effect showed a decrease over time ($p<.01$), indicating that the animals spent significantly less time moving as the time they spent in the monitor increased.

The interaction effect (lesion x time) was significant, as the lesioned only group was hyperactive ($p<.05$) compared to controls at minutes 30-40. At no time were the lesioned vs implanted animals, nor the lesioned vs controls, statistically different from each other. However, as can be seen in Figure 7, the lesioned only group were consistently more active than the other two groups from minutes 10-80.

(2) HORIZONTAL ACTIVITY

This is a measure of the total number of beam interruptions that

TABLE 10: MOVEMENT TIME (SECONDS)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	243723.456	2	121861.728	.935	
ERROR	2215891.480	17	130346.558		
WITHIN SUBJECTS					
TIME IN MONITOR	2657194.820	11	241563.165	21.050	.001
LESION X TIME	475601.170	22	21618.235	1.884	.012
ERROR	2145992.780	187	11475.897		

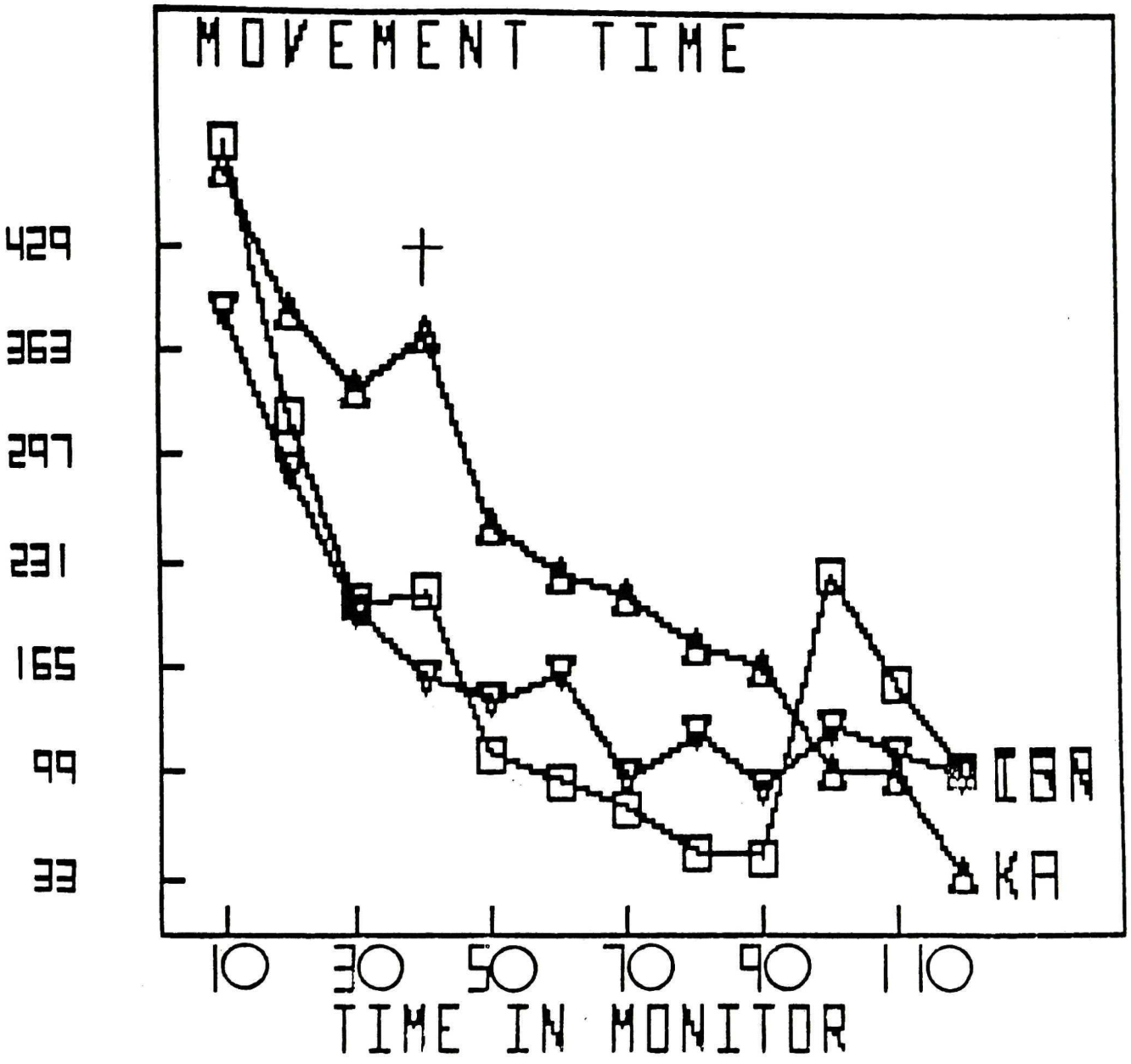


Figure 7: Mean number of seconds spent moving by the 3 groups of animals during the 120 minutes they were in the activity monitor. Squares are implanted, upward pointing triangles are lesioned only, downward pointing triangles are controls. +=$p < .05$, lesioned only vs. controls.

TABLE 11: HORIZONTAL MOVEMENTS

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	2904064.970	2	1452032.480	1.007	.388
ERROR	24525104.800	17	1442653.220		
WITHIN SUBJECTS					
TIME IN MONITOR	30434804.300	11	2766800.390	16.199	.001
LESION X TIME	6312152.140	22	286916.006	1.680	.034
ERROR	31939574.000	187	170799.861		

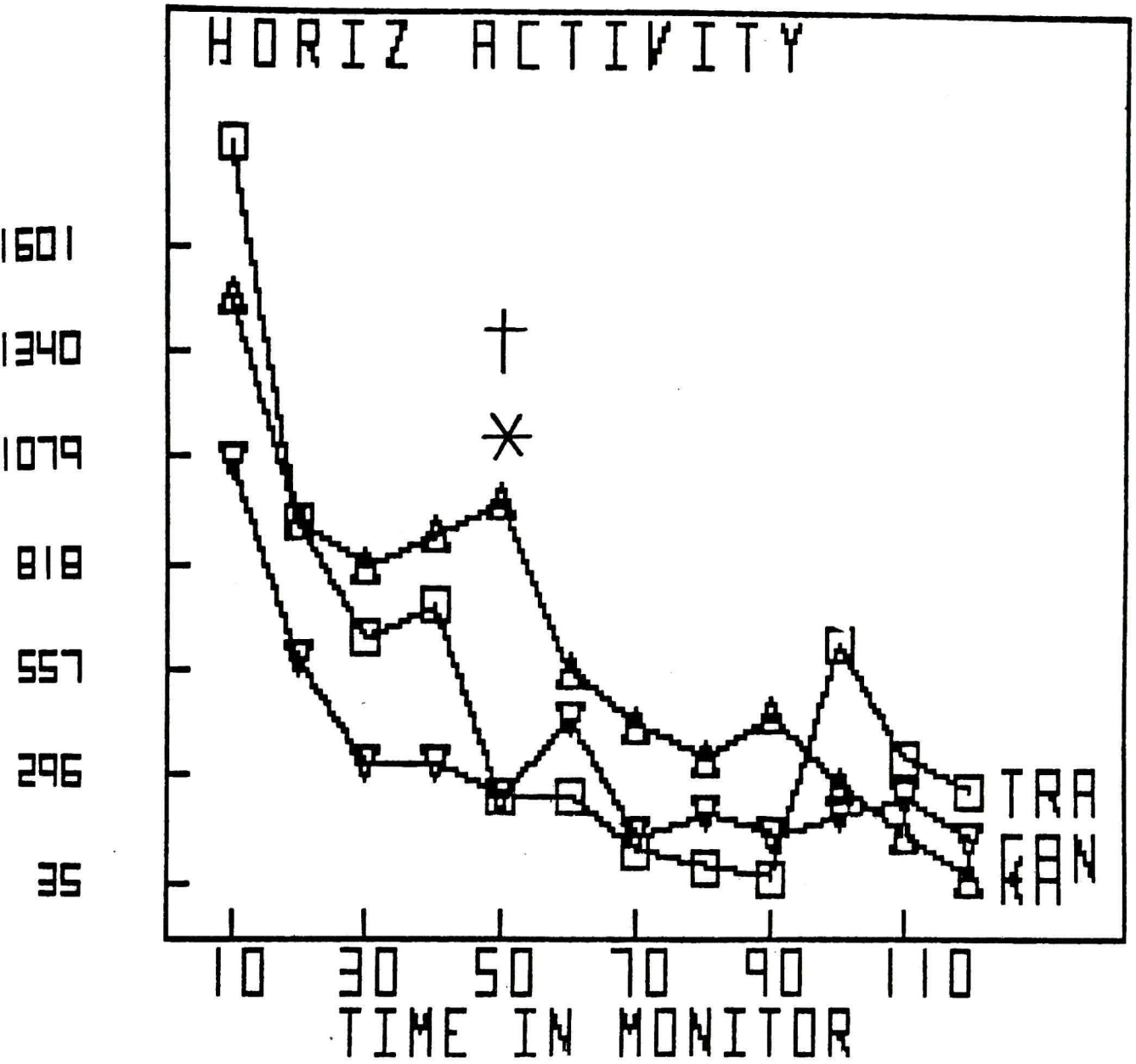


Figure 8: Mean number of horizontal movements emitted by the 3 groups of female Sprague Dawley rats over the 120 minutes they were in the activity monitor. Squares represent implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls. †=$p<.05$, lesioned only vs controls; *=$p<.05$, implanted vs controls.

occurred in the horizontal sensors while the animals were in the activity monitor. Table 11 shows the ANOVA summary for this measure. While the between subjects effect was nonsignificant, the repeated measures effect showed a significant decrease over time, indicating that animals had less horizontal activity as they spent increasing amounts of time in the monitor.

The lesion x time interaction effect was significant ($p=.034$). Two tailed Tukey post hoc comparisons indicated that the lesioned only animals showed more horizontal activity than controls at minutes 50-60 ($p<.05$). A priori t-tests revealed the lesioned only group to be more active than the implanted group also at minutes 50-60 ($p<.05$), while the implanted and control groups were not different. Although not statistically different, the lesioned only group again showed greater activity on this measure than the other two groups at minutes 30-90. These results are illustrated in Figure 8.

Thus the lesioned only group was hyperactive compared to both the implanted and control groups, while at no time was the implanted group different from controls.

(3) TOTAL DISTANCE

For each of the twelve, 10 minute time intervals the animals were in the activity monitors, the total inches travelled in the horizontal axis was recorded. The ANOVA summary is shown in Table 12. The repeated measures effect showed a decrease over time ($p<.01$), indicating that the animals spent significantly less time moving in the monitor as they spent increasing amounts of time in it.

While the between subjects effect was nonsignificant, the lesion

TABLE 12: TOTAL DISTANCE (INCHES)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	400659.114	2	200329.557	.402	
ERROR	8478552.820	17	498738.401		
WITHIN SUBJECTS					
TIME IN MONITOR	10220068.000	11	929097.093	20.007	.001
TIME X LESION	1833286.330	22	83331.197	1.794	.019
ERROR	8683933.950	187	46438.150		

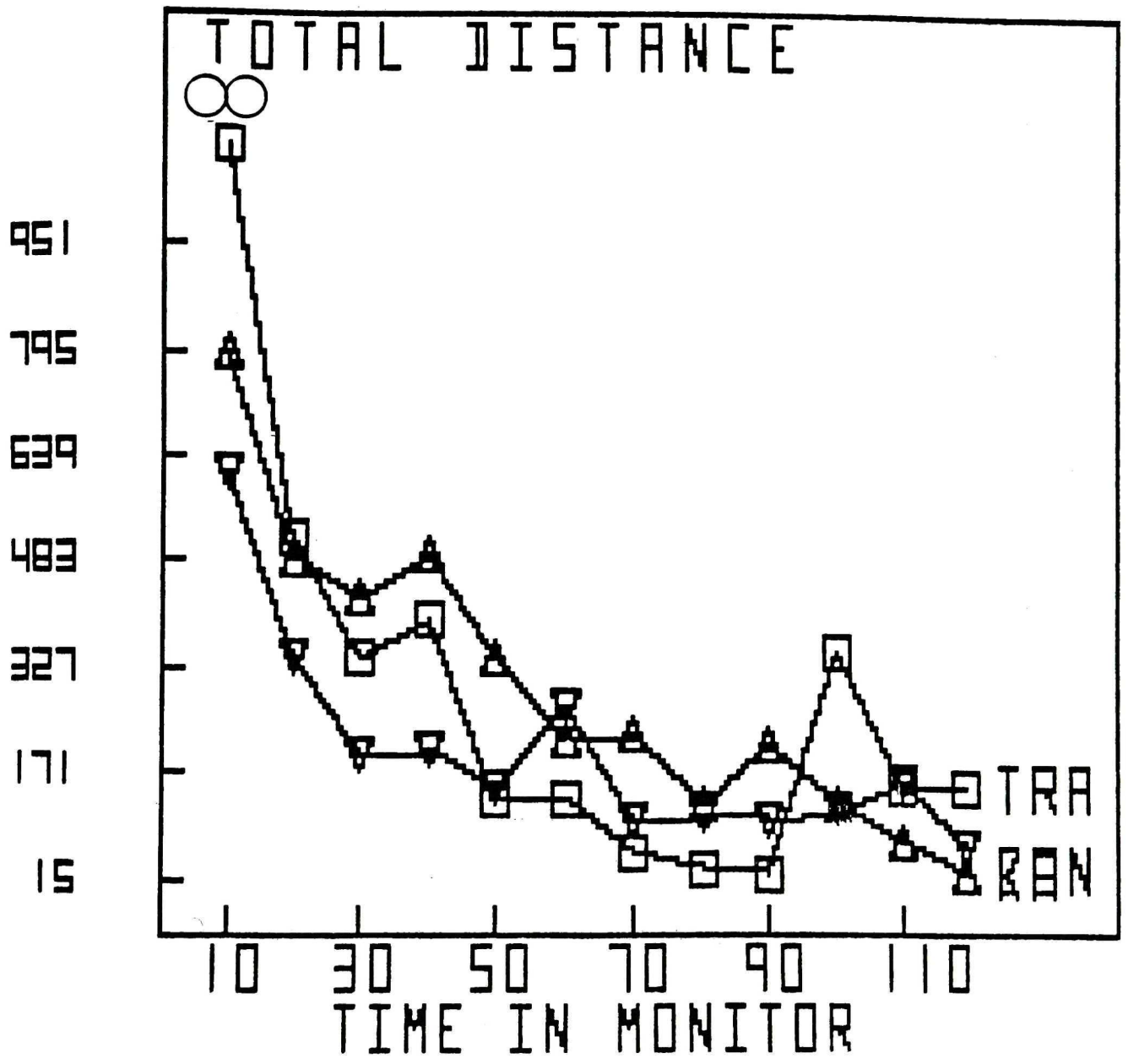


Figure 9: Mean number of inches travelled by each of the 3 groups of animals during their 120 minutes in the activity monitor. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls. oo=p<.01, implanted vs controls.

x time interaction showed a main effect ($p=.019$). Interaction comparisons revealed the implanted animals to be more active than controls ($p<.01$), but not lesioned only animals, during the first 10 minutes they were in the monitor. No significant differences were found between the implanted and lesioned only group, or the controls and lesioned only, at any time. Figure 9 shows the distance travelled by each group of animals over the 2 hours in the field.

(4) NUMBER OF STEREOTYPICAL MOVEMENTS

This is a measure of the number of repetitive, stereotypical movements emitted by each of the three groups of animals over the 2 hours they were in the monitor. The results from this behavior are illustrated in Table 13, and are atypical from the other locomotor measures in that the implanted group was hyperactive compared to both controls and lesioned only animals. As Figure 10 demonstrates, this hyperactivity occurred at minutes 10-20 and 30-40 ($p<.01$). Additionally, implanted animals were hyperactive to controls at minutes 20-30 ($p<.01$) and 50-60 $p<.05$), and to lesioned only at minutes 40-50 ($p<.01$). The lesioned only group was different from controls only at minutes 40-50 ($p<.01$).

Thus the implanted group was significantly more active than controls for 40 minutes, and lesioned only for 30 minutes on this measure, while the lesioned only group was statistically more active than controls only for 10 minutes.

TABLE 13: STEREOTYPY NUMBER

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	1667.344	2	833.672	5.036	.018
ERROR	2813.968	17	165.528		
WITHIN SUBJECTS					
TIME IN MONITOR	3757.531	11	341.594	13.458	.001
LESION X TIME	1021.077	22	46.413	1.829	.016
ERROR	4746.460	187	25.382		

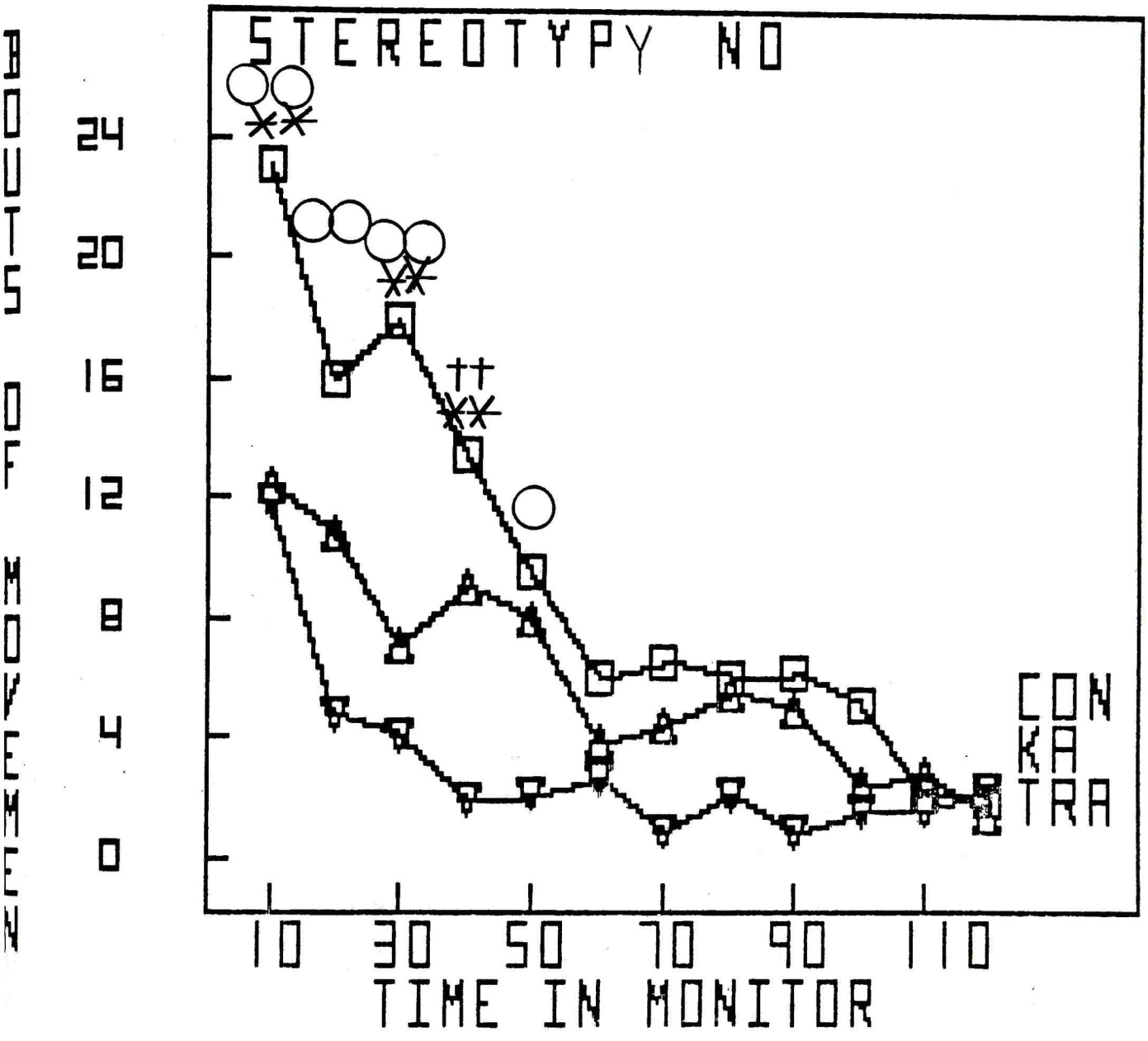


Figure 10: Mean number of stereotypic movements for each group of animals, plotted at 10 minute time intervals over the course of 2 hours. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls.

(5) STEREOTYPICAL MOVEMENT TIME

This is a measure of the amount of time spent moving in a stereotypical manner by each group of animals. Table 14 and Figure 11 illustrate the results from this measure. Although the implanted group showed more stereotypical movements than either of the other two groups, it did not spend significantly more time moving (in a stereotypical manner) than the controls. Rather, the lesioned only group was hyperactive compared to the other two groups. Between group contrasts revealed that the between group effect ($p=.051$) is a result of a hyperactivity by the lesioned only group compared to controls ($p<.02$; lesioned only vs implanted was nonsignificant). Interaction contrasts revealed the lesioned only group to be different from implanted rats at minutes 60-70 ($p<.05$) and 80-90 ($p<.01$), and different from controls at minutes 80-90 ($p<.01$).

This finding, taken together with that of the number of stereotypical movements, suggests that the lesioned rats moved much slower in their stereotypical movements, or emitted a different type of stereotypical movement, compared to implanted rats. The higher number of movements in the implanted group, combined with a normal amount of time moving, suggests that when they made repetitive movements, the implanted rats did so with a great velocity.

(6) NONSIGNIFICANT RESULTS

A number of the movement measures showed no significant between group or interaction effects. These included number of horizontal

TABLE 14: STEREOTYPICAL TIME (SECONDS)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	1464.371	2	732.186	3.525	.051
ERROR	3531.450	17	207.732		
WITHIN SUBJECTS					
TIME IN MONITOR	2674.826	11	243.166	1.418	.167
LESION X TIME	5130.824	22	233.219	1.360	.139
ERROR	32073.478	187	171.516		

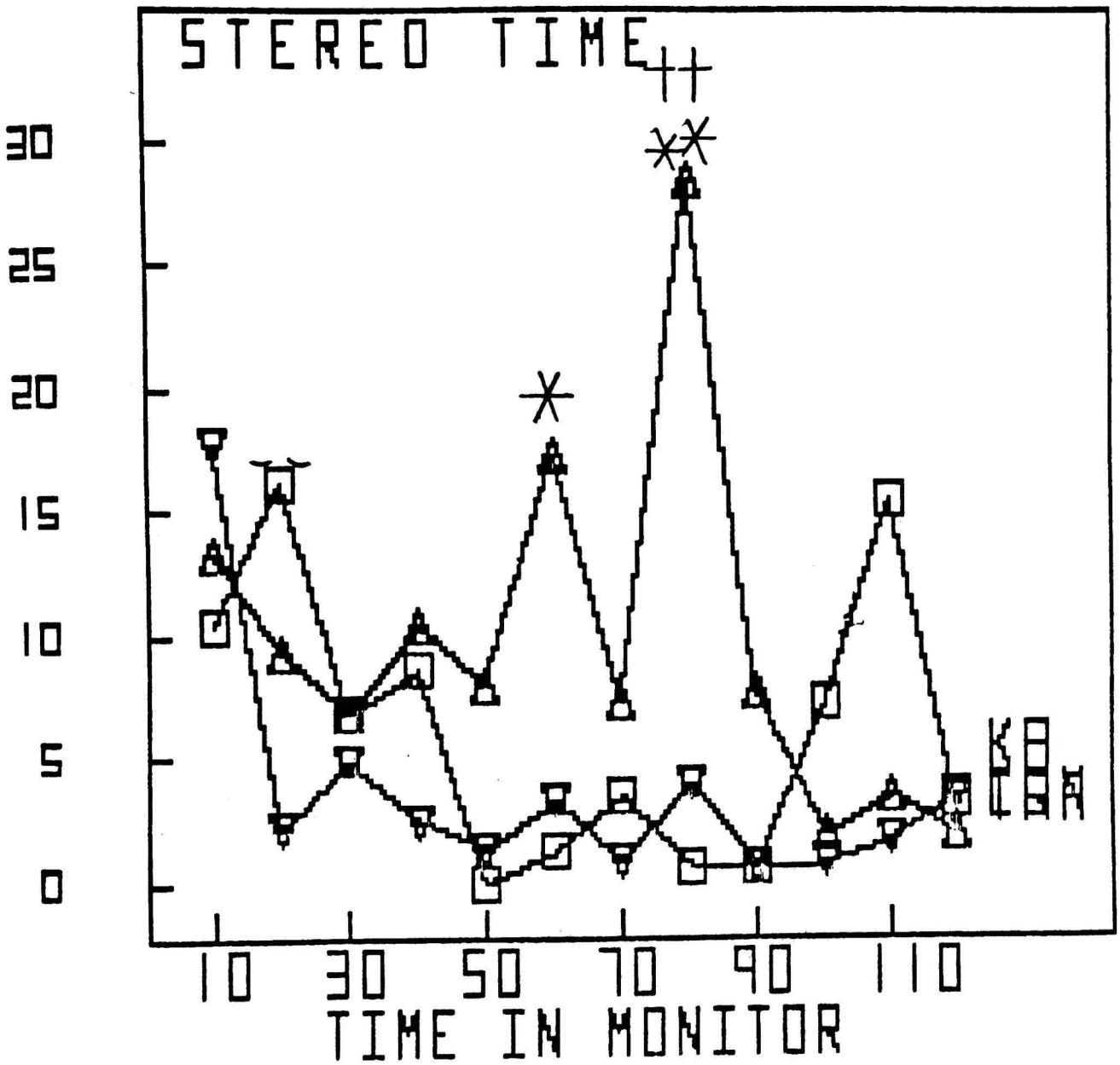


Figure 11: Mean number of seconds of stereotypic movements, plotted for each 10 minute interval the animals were in the monitor. Squares represent implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls. ++=$p<.01$, lesioned only vs. controls; *=$p<.05$, **=$p<.01$, implanted vs control.

movements, rest time, and all three of the vertical movement measures (i.e., vertical rears, vertical time, vertical activity). The graphs and tables from these measures are listed in Appendix E.

(7) SUMMARY OF SPONTANEOUS ANIMAL ACTIVITY

In summary, lesioned only rats were found to be statistically hyperactive compared to the controls group on several measures, including movement time, horizontal activity, stereotypical number, and stereotypical time.

Implanted animals, during their first 10 minutes in the monitor, appeared hyperactive relative to controls in several of the locomotion measures. This reached significance in two cases, including total distance and number of stereotypical movements. Aside from this, implanted animals were statistically different from controls only on number of stereotypical movements. However, implanted animals were also clearly different from lesioned only animals on stereotypical number, having a relative hyperactivity that gave the implanted group a significantly different profile from either of the other two groups.

Implanted animals were statistically different from lesioned only animals on horizontal activity, number of stereotypical movements, and stereotypical time. Thus the implants (1) led to a statistical recovery of deficits on horizontal activity and stereotypical time, (2) caused the implanted animals to behave in a unique way on stereotypical number, (3) failed to reverse a persistent hyperactivity during the first 10 minutes implanted animals were in the monitor, (4) led to no recovery on movement time, number of movements, rest time, vertical rears, vertical time, or vertical activity.

(b) NEUROLOGICAL EXAM

A neurological exam based on the battery used by Dunnett, Bjorklund, Stenevi, & Iversen (1981) was given to each animal 12 times, including presurgery, postsurgery, and once weekly for the 10 weeks following implantation. It systematically examined five different types of neurological functioning, including (1) muscle tone, (2) vibrassae and olfaction orientation (3) response to blunt touch (4) response to sharp touch, and (5) limb strength. From the data collected, a total score was computed for each of the 12 test administrations.

The scores on the neurological exam were analyzed by the use of a two factor ANOVA with 12 repeated measures. When the between group or within group effects were significant, a priori between group comparisons were done between the implanted and lesioned only groups, and the implanted and control groups (notated as a "t" statistic). In addition, post hoc comparisons (done according to a Tukey ratio, notated as a "q" value) were done comparing the lesioned only group with the control group.

Figure 12 shows the results from the neurological exam. There was no difference between groups presurgery (week one on Figure 12). However, following lesioning with kainic acid at week 2 there was a large and persistent deficit in both the lesioned only ($p<.01$) and implanted ($p<.02$) groups compared to controls. The between group effect was highly significant ($p<.005$) as shown in Table 15. There was no significant difference between the lesioned only and implanted groups. Contrasts done on the interaction effect found no significant differences at any time between the implanted and lesioned only group. However, the implanted animals were significantly different from

TABLE 15: TOTAL NEUROLOGICAL SCORE

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	5415.08	2	2707.54	7.140	.005
ERROR	6447.25	17	379.25		
WITHIN SUBJECTS					
WEEKS	1954.39	11	177.67	6.660	.001
LESION X WEEKS	1131.67	22	51.44	1.923	.010
ERROR	4988.55	187	26.67		

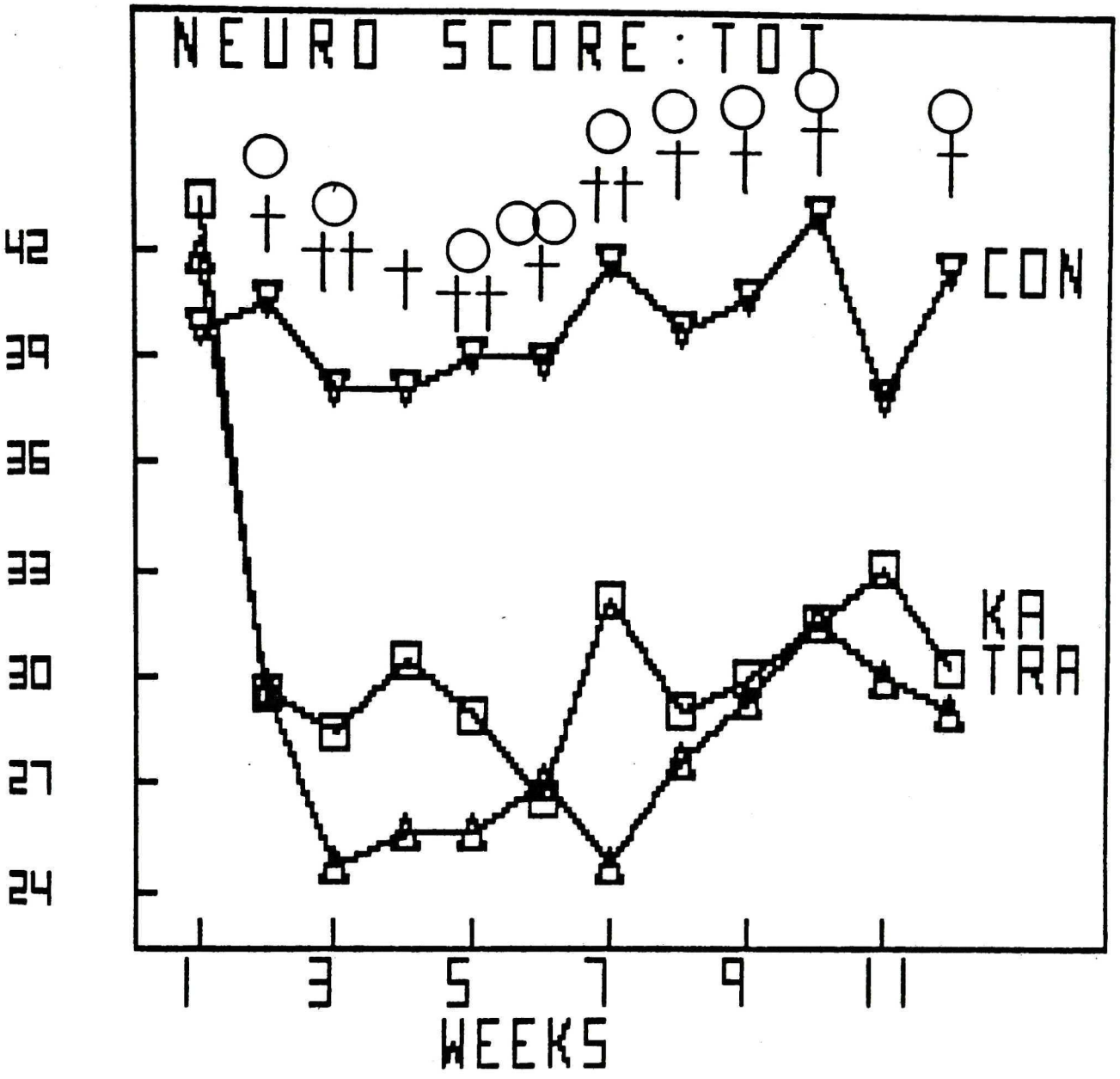


Figure 12: Mean total neurological score for female Sprague Dawley rats pre surgery (week 1), post kal (week 2), and for 10 weeks post implantation (weeks 3-12). Squares are implanted animals, upward pointing triangles are lesioned only, and downward pointing triangles are controls. +=$p < .05$, ++=$p < .01$, kal vs. control; o=$p < .05$, oo=$p < .01$, implanted vs. control.

However, the implanted animals were significantly different from controls at weeks 2, 3, 5, 7-10, and 12 ($p<.05$), at week 6 ($p<.01$), and not significantly different at weeks 4 and 10. Kainic acid lesioned animals were significantly different from controls at weeks 3, 5, and 7 ($p<.01$), and weeks 2, 4, 6, and 8-12 ($p<.05$). Thus both lesioned only and implanted rats showed a profound and enduring deficit on the neurolgical exam.

(C) DELAYED REWARDED ALTERNATION (T-MAZE)

Rats were trained on a simple T-maze task prior to surgery until they alternated 85% of the time or more for 3 consecutive days. Twelve weeks after implantation or sham implantation, the animals were rerun without any pretraining on the maze for 10 consecutive days (20 trials per day).

Presurgery trials to criteria were calculated for each rat by multiplying the number of days to criteria by 20 (i.e. the number of daily trials). There was no significant difference between groups on presurgery performance, as shown below.

TRIALS TO CRITERIA

BETWEEN:	SS=38577.69	DF=2	MS=19288.85	F=1.02
WITHIN:	SS=321492.8	DF=17	MS=18911.34	
TOTAL:	SS=360070.5	DF=19		

During the postsurgery training, daily correct alternations were computed for each rat for each of the 10 days of maze running. A two factor split plot ANOVA with 10 repeated measures was used to analyze the data. Between group and interaction effect comparisons were done as described previously.

Between group ($p=.041$), repeated measures ($p=.048$), and interaction effects ($p=.021$) all were significant, as shown below. Between group contrasts revealed the lesioned only group to be significantly different from controls ($p<.02$), while the implanted group was not statistically different from either the control or lesioned only groups.

As shown in Figure 13, the average correct number of responses in the control group exceeded the lesioned only group for all 10 sessions, and the implanted group on 9 of the 10 sessions. Conversly, the implanted group outperformed the lesioned only group on 9 of 10 sessions. The difference between the control and lesioned only group reached significance on sessions 4 ($p<.05$), 5 ($p<.01$), and 6 ($p<.05$). The implanted group alternated statistically more often than the lesioned only group during session 3 ($p<.05$), while the implanted animals alternated statistically less often than controls on session 9.

The total number of perseverative responses emitted by each animal (i.e. the number of times it visited the same arm on three or more consecutive visits) were counted for each of the 10 sessions of postimplantation maze running, and cumulated to give each animal a postsurgery perseveration score. Similarly, the total number of perseverations emitted by each animal during their presurgery training was obtained. A one-way ANOVA found that the groups did not differ in

T-MAZE

OF CORRECT ALTERNATIONS

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	409.904	2	409.904	3.835	.041
ERROR	1816.855	17	106.874		
WITHIN SUBJECTS					
SESSIONS	126.705	9	14.078	1.949	.048
LESION X SESSIONS	244.235	18	13.569	1.878	.021
ERROR	1105.455	153	7.225		

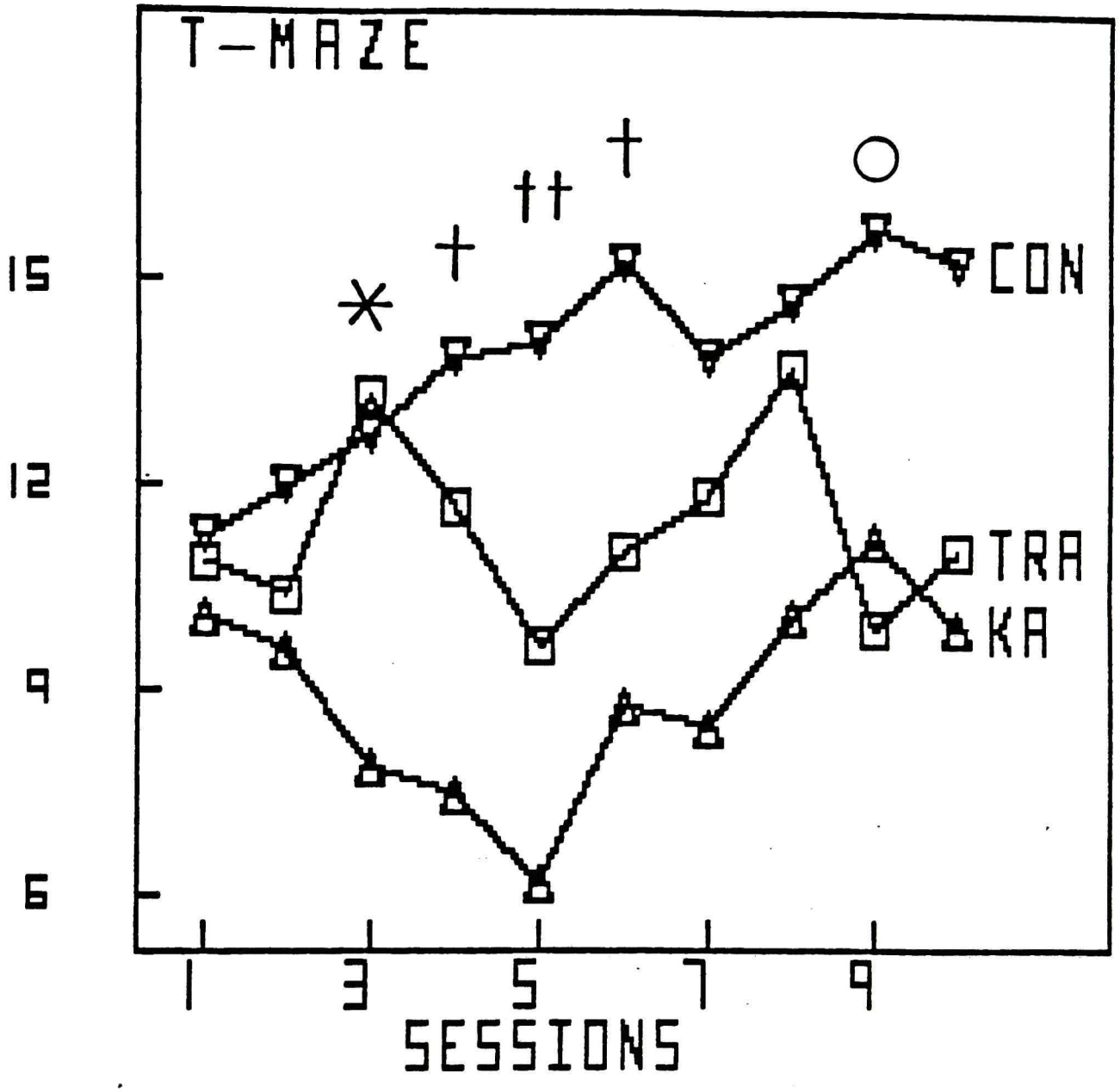


Figure 13: Average number of correct alternations (out of a possible 20) emitted by each group during the 10 days of post surgery T-maze running. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls. +=$p<.05$, ++=$p<.01$, lesioned only vs. controls; *=$p<.05$, lesioned only vs implanted; o=$p<.05$, implanted vs. controls.

their perseverative behavior either pre- or postsurgery, as Tables 16 and 17 illustrate.

TABLE 16: PRESURGERY T-MAZE PERSEVERATIONS

BETWEEN:	SS=137.56	DF=2	MS=68.78	F=.625
WITHIN:	SS=1868.2	DF=17	MS=109.9	
TOTAL:	SS=2005.7	DF=19		

TABLE 17: POSTSURGERY T-MAZE PERSEVERATIONS

BETWEEN:	SS= 4604.66	DF=2	MS= 2302.33	F=1.96
WITHIN:	SS=19950.28	DF=17	MS= 1173.54	
TOTAL:	SS=24554.9	DF=19		

Because there were large changes within groups in their perseverative behavior pre- and postsurgery, correlated t-tests were done for each of the three groups of animals by comparing presurgery levels of perseveration with postsurgery levels. As shown in Table 18, the lesioned only group emitted more perseverations postsurgery ($p<.01$), while neither the control nor implanted groups showed pre-post differences. Although not statistically significant, the implanted

group did show a four-fold increase in number of perseverations pre vs postoperatively (p=.10).

TABLE 18: CORRELATED T-TESTS---PRE AND POST PERSEVERATION SCORES

	PRE		POST		t	p
	mean	s.d.	mean	s.d.		
IMPLANTED	10.3	4.5	42.0	38.1	1.99 (6df)	=.10
LESIONED ONLY	11.3	5.5	57.3	23.0	4.84 (7df)	<.01
CONTROLS	16.3	16.3	21.1	39.8	0.27 (7df)	ns

To assess if the increased number of lesion induced perseverations were simply a function of increased mistakes, for each animal the number of perseverations were divided by the number of mistakes and multiplied by 100 to give a percent perseveration score. Means and standard deviations from this calculation are presented in Table 19.

TABLE 19: PERCENT PERSEVERATIONS

	mean	s.d.
IMPLANTED	41.7%	19.5
LESIONED ONLY	50.1%	13.0
CONTROL	21.1%	24.0

As shown in the table, 50% of the mistakes in the lesioned only group, 42% of the implanted group's, and 21% of the control group's mistakes occurred as perseverative responses. Thus the perseverations do not appear to be only a function of number of mistakes, but rather occur as a consequence of the lesions.

In summary, the lesioned only animals were significantly impaired in their ability to correctly alternate in the maze in comparison to controls, doing worse on the maze for each of the 10 postsurgery sessions. In addition, the lesioned only animals perseverated frequently, leading their maze performance to appear qualitatively as well as quantitatively different from controls.

The implants led to partial recovery from the T-maze deficit. Although on the average the implanted group performed worse than controls on 9 of the 10 sessions, this reached significance only in

session 9 ($p<.05$). The implanted group on the average outperformed the lesioned only group also for 9 sessions, performing statistically better in session 3 ($p<.05$). On the between group comparisons, the lesioned group was significantly worse than the controls, while the implanted group was nonsignificantly different from both of the other groups. Finally, the implanted group did not perseverate statistically more often after surgery than before, although many of their mistakes were perseverative in nature during the postsurgery T-maze trials. Thus the implanted animals, while performing poorly on this task in comparison to controls, were slightly improved on this measure compared to the nonimplanted group.

(d) BODY WEIGHTS OF ANIMALS

(1) WEIGHT GAINS OVER THE COURSE OF THE EXPERIMENT

Animals were weighed each week early in the morning, starting for the week prior to kainic acid surgery, and continuing for 12 weeks after implantation. Mean weekly weights were obtained for each group, and plotted for 12 weeks, as shown in Figure 14. A one-way ANOVA done on the prelesion weights revealed there to be no significant differences between groups, as shown in Table 20.

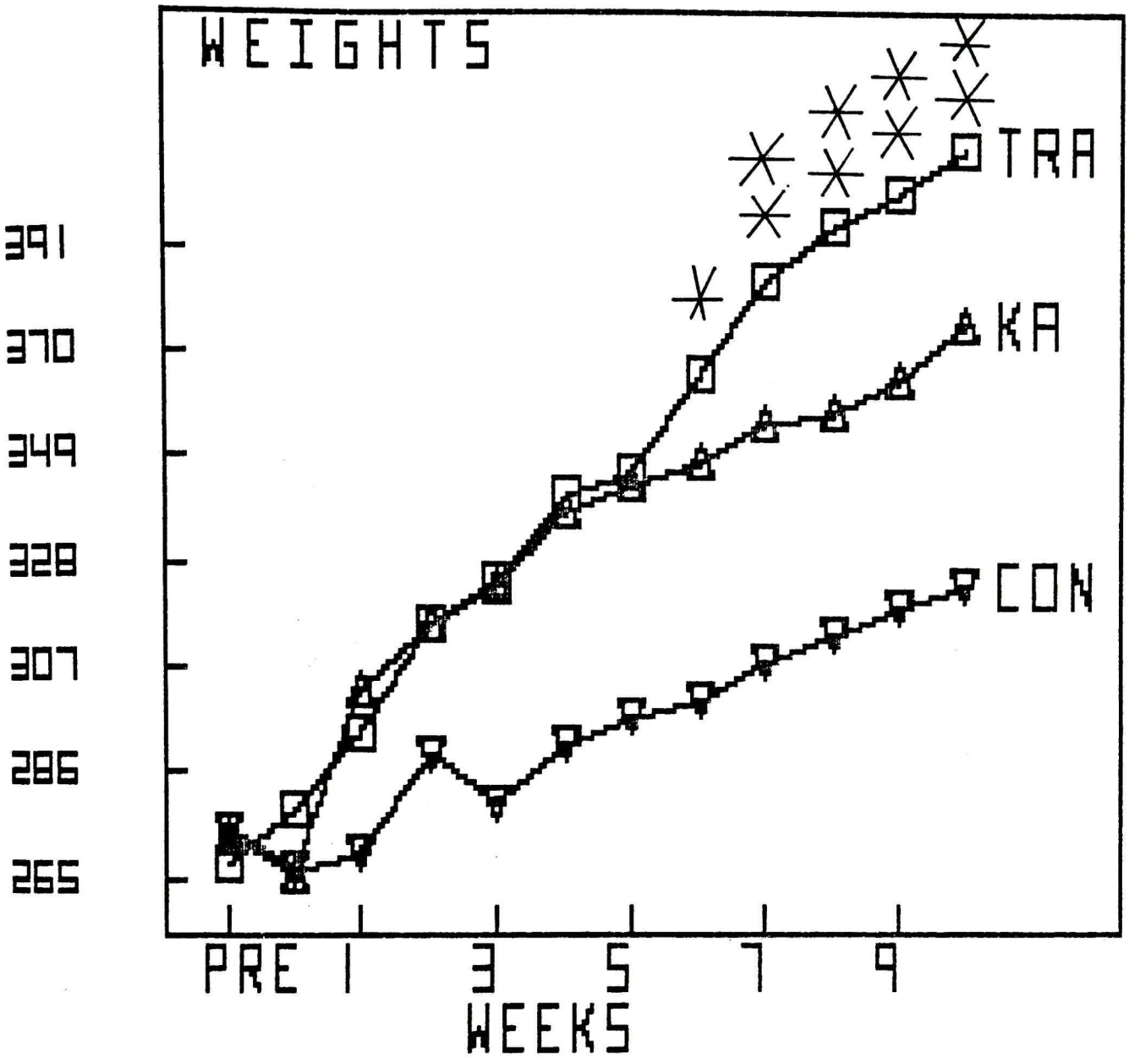


FIGURE 14: Mean weekly weights pre and post kals, and for the 10 weeks following implantation. Squares are implanted, upwards pointing triangles are lesioned only, and downward pointing triangles are controls. *=p .05, **=p .01, implanted vs controls.

TABLE 20: PRELESION WEIGHTS (GRAMS)

	SS	DF	MS	F	P
BETWEEN	191.33	2	95.66	.2	ns
WITHIN	6177.62	17	363.39		

MEAN WEIGHTS (GRAMS)

IMPLANTS	267.3
LESIONED ONLY	273.1
CONTROL	274.7

A two factor split plot factorial ANOVA with 12 repeated measures was performed on the weights for the 12 weeks after implantation (NOTE: the prelesion weights were run separately from this analysis only because the system analyzing this data could accomodate a maximum of 12 repeated measures). Main effects and simple main effects were highly significant, as presented in Table 21. A priori between group comparisons revealed the implanted group weighed significantly more than controls ($t=3.08$; $df=17$; $p<.01$), while the implanted vs lesioned only comparison ($t=.89$; $df=17$) was nonsignificant. The a posteriori lesioned only vs control comparison also was nonsignificant ($q=2.27$; $df=17$).

Comparisons done on the interaction effect indicated that the

TABLE 21: WEIGHTS OBTAINED FROM WEEKS 1-12 AFTER IMPLANTATION/SHAM IMPLANTATION (GRAMS)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	164707.069	2	82353.535	5.07	.018
ERROR	276049.586	17	16238.211		
WITHIN SUBJECTS (REPEATED MEASURES)					
TIME	181184.399	11	16471.309	39.016	.001
LESION X TIME	21482.631	22	976.483	2.313	.001
ERROR	78944.512	187	422.163		

implanted group became heavier compared to controls starting at week 6 after implantation ($p<.05$), and increased in significance from weeks 7-12 after implantation ($p<.01$, see Figure 14). At no time was the lesioned only group significantly different from either of the other two groups.

In summary, the kainic acid lesioned only group nonsignificantly increased their weight compared to controls. Although the implanted group was indistinguishable from the lesioned group for the first 5 weeks after implantation, they suddenly and sharply increased their weight for a 2 week period beginning at week 6 after implantation, and then maintained this weight gain for the remainder of the experiment. This increased weight gain resulted in the implanted group being significantly heavier than controls for the last 6 weeks of the experiment, while at no time was the lesioned only group statistically different from either of the other two groups. This finding was unexpected, and was not detected until the end of the experiment, after many of the animals had been sacrificed for histology. In order to make a preliminary attempt to investigate the etiology of the weight differences, two additional manipulations were performed on the remaining animals, which included three transplanted, four lesioned only, and three controls.

(2) AD LIB AND INSULIN AFFECTED EATING AND DRINKING

Seven days after finishing the T-maze postoperative running, ad lib food and water consumption were measured for one 24 hour period for the surviving animals, which included three transplanted, four lesioned only, and three controls. All other animals had been sacrificed before

the weight effect had been noted. To assess food consumption, animals (one per cage) had their bedding removed, and an empty metal food cup was placed under a suspended metal food rack. This allowed for measurement of both eaten, and spilled, food. The food weights were measured on a balance (Fisher) sensitive to 0.10 grams. Simultaneously, 100 mls water bottles, calibrated to 1.0 ml., were added to each cage to measure water consumption. Immediately following this, 2 units/kg of regular insulin were injected subcutaneously into the animals (Ritter, Roethke, & Neville, 1978), and food and water consumption were measured for the 24 hours after the injection. Finally, the 24 food and water consumption for the day after injection was measured. Thus food and water consumption was measured for the 24 hours before, during, and after insulin injection.

The insulin injections were given in an attempt to better understand the causes for the weight gains in the implanted group. It was hypothesized that the weight gain might be secondary to changes in centrally mediated glucose and/or insulin receptor sensitivity due to the effects of the fetal implants. The insulin challenge was done to assess if the implants had caused an increased number of these receptors, or had increased their sensitivity. If the implants had caused such changes, then activation of these receptors by systemic injection of insulin would be expected to lead to increased eating behavior, as the implanted animals would be particularly sensitive to changes in blood glucose and/or insulin levels. Previously, it has been shown that systemic insulin injections lead to increased eating in rats whose glucoreceptors had been pharmocologically rendered less sensitive by deoxyglucose administration, with the rats eating less food in response to insulin injection after the deoxyglucose administration

(Ritter et al., 1978).

Table 22 shows the results from the two factor analysis of covariance run on the data for 24 hour water consumption. This analysis compared 24 hours of water ingestion for the day prior to insulin injection, during insulin injection, and following injection across three controls, three implanted, and four lesioned only animals. Weight was controlled for in the analysis by factoring it as a covariate, on the assumption that heavier animals would eat more in order to maintain their weight. A significant between group effect was found. Between group comparisons revealed that the implanted group drank significantly more than controls ($t=4.05$; 8 df; $p<.05$), while the lesioned only group was not statistically different from either of the other two groups. These effects are shown in Figure 15.

Conversely, there were no significant differences between groups on 24 hour food consumption, either pre, post, or on the day of insulin injection. The graphs and ANOVA tables from this measure are presented in Appendix F. Thus while the implanted group drank more than controls, they did not eat significantly more.

(3) EFFECT OF FOOD DEPRIVATION ON EATING AND DRINKING

To assess if the difference in water consumption was related to prandial (i.e., food accompanied) drinking, a second feeding manipulation was performed on these surviving animals (i.e., three transplanted, four lesioned only, and three controls). Four days following the insulin administration, all animals were food deprived for 24 hours. Immediately upon completion of this deprivation, animals were fed <u>ad lib</u> for 24 hours, and the amount of food and water consumed was

TABLE 22: 24 HOUR WATER CONSUMPTION BEFORE, DURING, AND AFTER INSULIN INJECTION (MLS)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	999.395	2	499.698	4.57	.047
ERROR	874.295	8	109.287		
WITHIN SUBJECTS					
24 HOUR FLUID CONSUM.	82.873	2	41.436	1.07	.364
LESION X 24 HR CONSUM.	211.29	4	52.823	1.366	.284
ERROR	696.02	18	38.668		

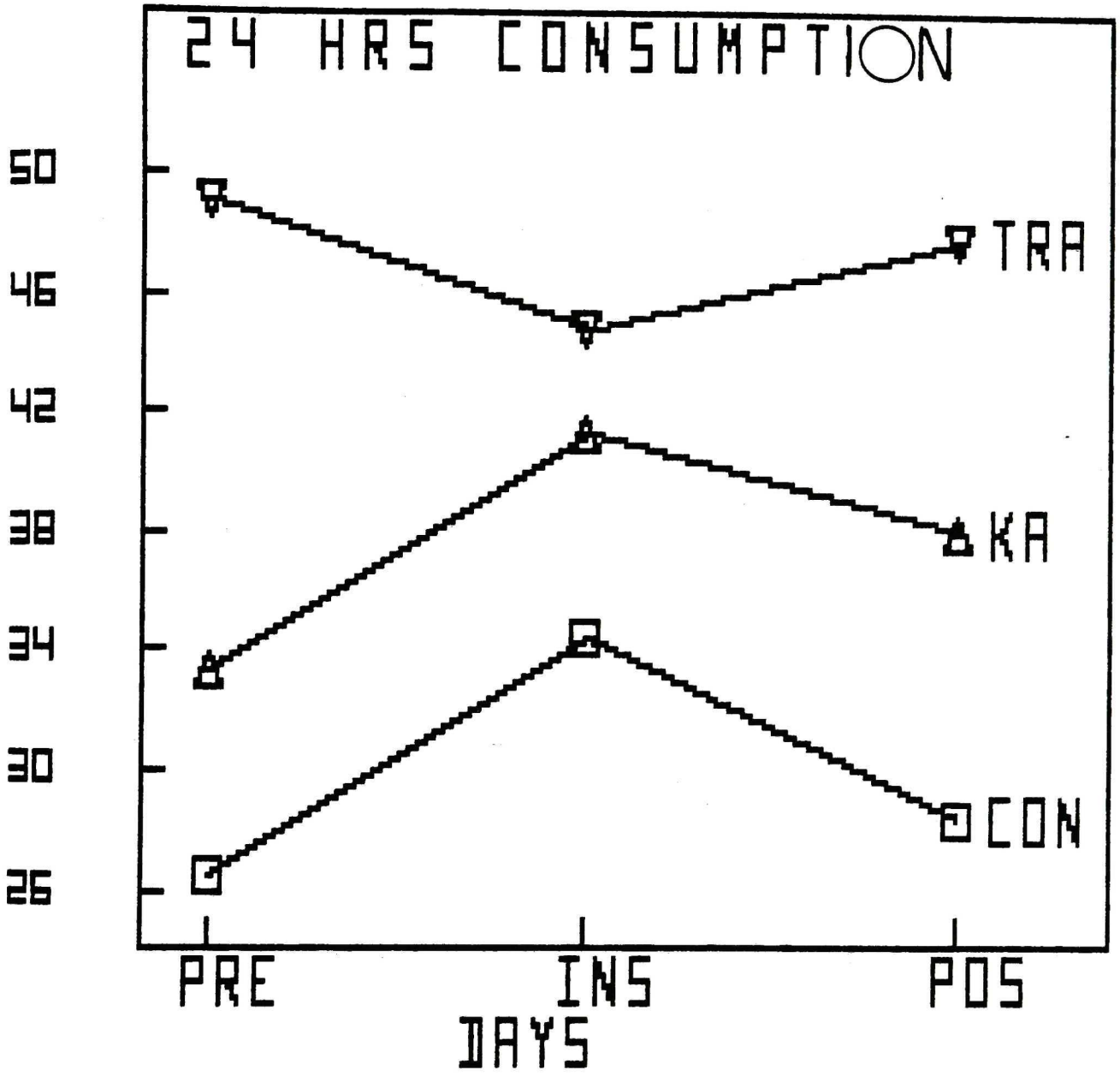


FIGURE 15: Mean 24 hour water consumption prior to, during, and post insulin injection. Downward pointing triangles are implanted, upward pointing triangles are lesioned only, and squares are controls.

measured, as described before. Four measures were obtained. First, water consumption was measured for the 24 hour period during food deprivation, and for the 24 hours on the day after ad lib feeding, via the use of water bottles calibrated to 1.0 ml. Secondly, weight loss during the 24 hours of food deprivation was recorded. Finally, food consumption was measured, as described above. Measurements were taken both during the first hour, and for the 24 hours after reinstatement of eating was obtained.

An analysis of covariance was done on the water consumption for the 24 hours during and after food deprivation. There were no significant effects found on this measure. The ANOVA tables from this measure are presented in Appendix F.

Weight loss by each animal during the 24 hours of food deprivation was also measured. Each animal was weighed prior to, and immediately after, 24 hours of food deprivation, and weight loss was compared between groups. When initial weight of the animals was covaried against weight loss, the control group was found to lose more weight during 24 hours of starvation than either of the other two groups, as Table 23 illustrates.

Planned comparisons revealed that both the implanted ($t=5.40$; 6 df; $p<.01$) and lesioned only ($q=5.80$; 6 df; $p<.05$) groups lost significantly less weight than controls for this time period. Thus the control animals lost more weight per gram of body weight during the 24 hours of food deprivaton.

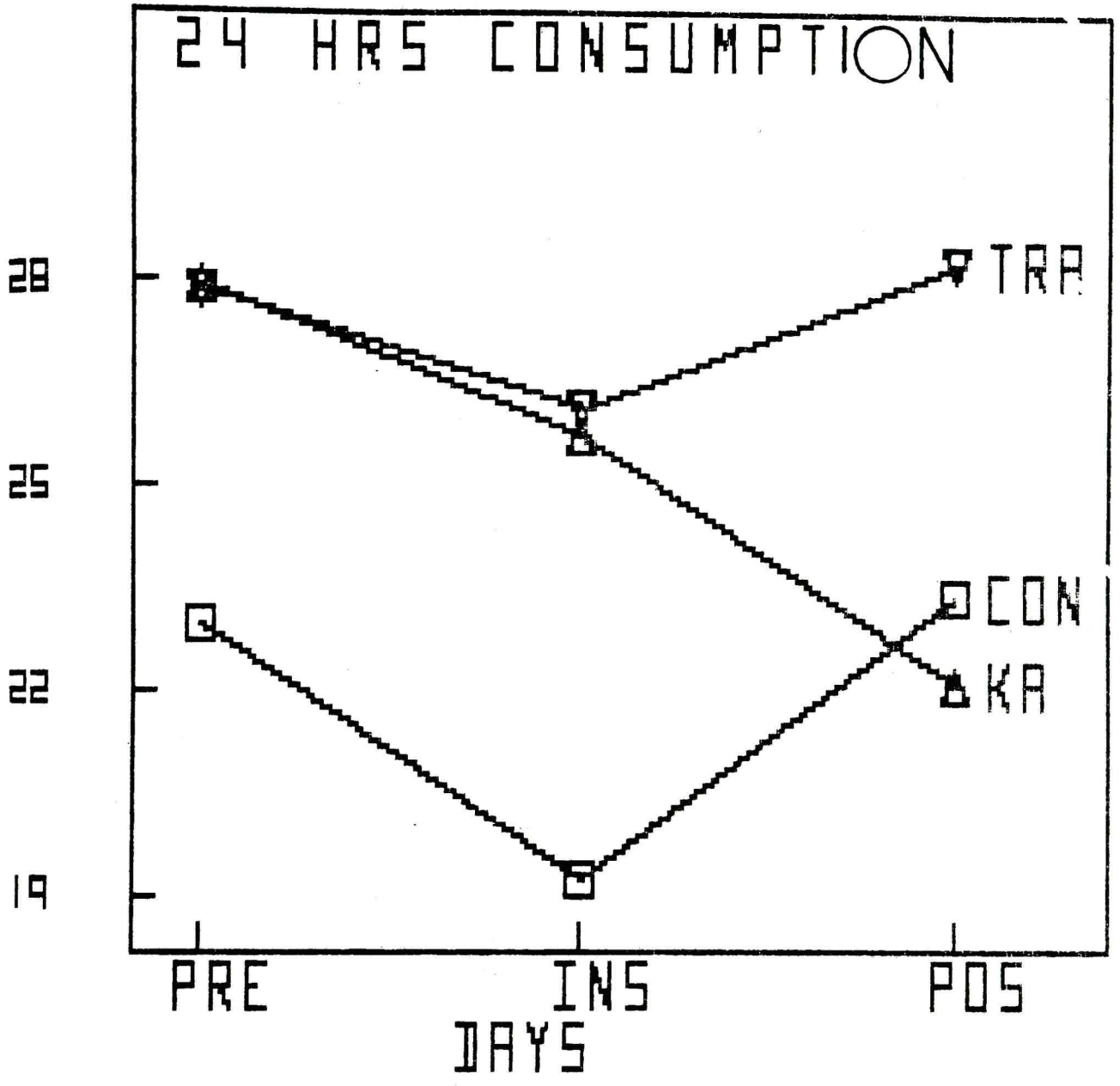


Figure 16: Mean 24 hour food consumption prior to, during, and post insulin injection. Downward pointing triangles are implanted, upward pointing triangles are lesioned only, and squares are controls.

TABLE 23: ONE-WAY ANALYSIS OF COVARIANCE OF WEIGHT LOSS DURING 24 HOURS OF FOOD DEPRIVATION

	SS	DF	MS	F	p
BETWEEN	119.7	2	59.8	14.6	<.01
WITHIN	24.5	6	4.09		

adjusted means of weight loss

implanted	11.99 grams
lesioned only	16.79 grams
controls	25.30 grams

(4) FOOD CONSUMPTION

Food consumption was measured for the first hour, and for the first 24 hours, after the 24 hour food deprivation period ended and the ad lib eating began.

The amount of food consumed did not differ between groups for the first hour, as shown in Table 24.

TABLE 24: ONEWAY ANALYSIS OF COVARIANCE FOR FOOD EATEN DURING THE FIRST HOUR AFTER FOOD DEPRIVATION ENDED

	SS	DF	MS	F	p
BETWEEN	6.09	2	3.04	.67	ns
WITHIN	27.17	6	4.53		

However, there was a significant difference between groups on the amount of food eaten during the 24 hour period of ad lib feeding, as shown in Table 25.

TABLE 25: ONEWAY ANALYSIS OF COVARIANCE FOR FOOD EATEN DURING THE FIRST 24 HOURS AFTER FOOD DEPRIVATION ENDED

	SS	DF	MS	F	P
BETWEEN	267.7	2	133.87	6.24	<.05
WITHIN	128.6	6	21.43		

adjusted means of food consumed (grams)

implanted	21.94
lesioned only	34.32
controls	27.13

A priori contrasts between the lesioned only and implanted group revealed the lesioned animals to eat significantly more than transplanted animals ($t=3.32$; 6 df; $p<.02$). The controls were not significantly different from either of the other two groups. Thus following availability of food after a 24 hour period of starvation, the lesioned only animals ate significantly more than controls.

(5) POSTMORTEM FINDINGS

Brief postmortems were done on all groups of animals involved in the feeding experiments. They showed that the implanted animals, and to a lesser extent the lesioned only animals, had large mesenteric and subcutaneous fat deposits. It was not possible to examine the intestines of these animals without first stripping from this region beady sheets of white adipose tissue. Additionally, subcutaneous fat deposits, both in the abdominal region, and in the neck pad, were larger than normal. No other obvious abnormalities of the intestines, heart, lungs, liver, or kidneys were noted during these examinations.

(6) SUMMARY OF WEIGHT FINDINGS

In summary, the kainic acid lesions caused a nonsignificant weight increase in the lesioned only group. This increase began shortly following lesioning, and then plateaued and remained constant for the remainder of the experiment. The implanted animals also showed this gradual increase in weight gain over controls for the 5 weeks following kainic acid lesions. However, at week 6, they showed an increase in

weight over the lesioned only group that continued for 2 weeks, and then plateaued and remained constant for the remainder of the experiment. This led the implanted group to become significantly heavier than controls. The lesioned only group was not significantly different from either of the other two groups, but by the end of the experiment fell midway in weight between the other two groups.

Measurements of the feeding behavior showed that neither the lesioned only nor implanted animals ate significantly more than controls ad lib, although a nonsignificant trend in this direction existed. However, the implanted group drank more ad lib than the control animals, while the lesioned only group drank midway between the controls and the implanted group. Insulin injections did not differentially affect either eating or drinking behavior.

When animals were food deprived, the controls lost more weight than both of the other two groups, suggesting that the weight gains seen in the implanted group could be due to decreased metabolic activity caused by the lesion/implants. Additionally, during food deprivation, both lesioned and implanted groups showed a nonsignificant trend towards having more non-prandial drinking than controls.

The only significant difference noted between the lesioned only and implanted groups occurred after 24 hours of food deprivation. Lesioned only animals ate significantly more than the implanted animals during the 24 hours after ad lib feeding was reinstated.

Thus in comparison to controls, the implanted animals were statistically heavier, drank more water ad lib, and lost less weight during 24 hours of starvation. The lesioned only group showed trends in the same direction on these measures, but were only significantly different from controls in weight lost during starvation. Finally, the

implanted animals were statistically different from the lesioned only group in that they ate less when ad lib food was made available following 24 hours of starvation.

(e) OPEN FIELD

Each animal was placed in the open field five times during the course of the experiment, including prior to the kainate lesions, and at 2 weeks, 6 weeks, 10 weeks, and 14 weeks after implantation/sham implantation. Each time the animal was placed in the field, horizontal activity (measured by counting the number of squares crossed by the animal) and vertical activity (measured by the number of rears the animals made) were assessed both under spontaneous movement conditions, and in response to amphetamine injections. Spontaneous movement was measured during the first 5 minutes the animals were in the field, and one hour later for 5 minutes, after the animals had habituated to the field. Locomotor activity in response to amphetamine was measured at minutes 5-10, 20-25, and 55-60 after the amphetamine injection.

Results were analyzed with two factor split plot ANOVAS with five repeated measures. Where significance was detected, planned comparisons were done between implanted vs controls, and implanted vs lesioned groups. A posteriori contrasts were done between the lesioned only group and controls.

(1) SPONTANEOUS HORIZONTAL ACTIVITY

(i) MINUTES 0-5

Squares crossed during the first 5 minutes the animals were in

TABLE 26: MINUTES 0-5 IN OPEN FIELD:
OF SQUARES CROSSED

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	79879.122	2	39939.561	3.41	.05
ERROR	199231.811	17	11719.518		
WITHIN SUBJECTS (REPEATED MEASURES)					
WEEKS	52039.793	4	13009.948	3.46	.012
LESION X WEEKS	36433.072	8	4554.134	1.21	.304
ERROR	255395.617	68	3755.818		

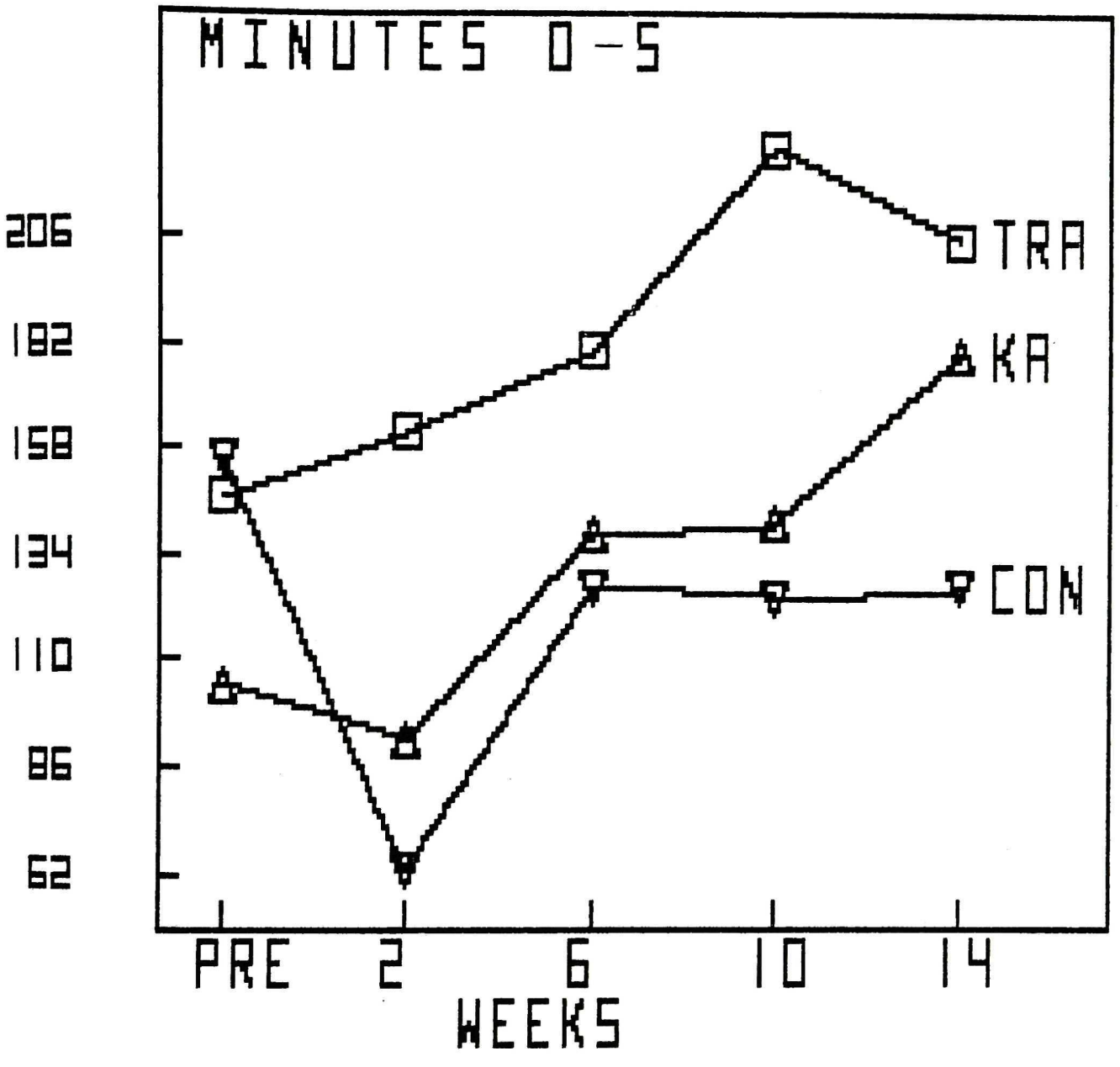


FIGURE 17: Mean number of squares crossed during the first five minutes that the animals were in the open field. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls.

the open field were assessed accross the five testing sessions. There was a significant between group ($p=.05$) and repeated measures ($p=.012$) effect, as shown in Table 26 and Figure 17. Between group comparisons found that the implanted group was more active than controls ($t=2.42$; 17 df; $p<.05$), and nonsignificantly different from the lesioned only group ($t=.81$; 17 df).

Within group comparisons were made to see if any of the three groups changed in their spontaneous horizontal activity from week 2 after implantation to week 14. This was done to assess if the kainic acid lesions caused a progressive hyperactivity over time. Although all groups became more active over the course of the experiment (see Figure 45), no group was hyperactive at week 6, 10, or 14 in comparison to week 2.

In summary, the implanted group showed a hyperactivity in comparison to controls during the first 5 minutes they were in the open field. The activity level of the lesioned only group fell nonsignificantly between that of the other two groups.

(ii) MINUTES 55-60

There were no significant differences between groups at any of the five time periods. The ANOVA table and accompanying graph of this measure are listed in Appendix G.

(2) HORIZONTAL ACTIVITY POST AMPHETAMINE INJECTION

(i) MINUTES 5-10

There were no significant between group differences in horizontal

activity during minutes 5-10 post amphetamine injection, as shown on Table 27. All groups did show an increased response to amphetamine over the course of the experiment ($p<.001$), which peaked after their fourth injection at week 10. This effect is shown in Figure 18. However, no group was hyperactive at weeks 6, 10, or 14 in comparison to week 2.

(ii) MINUTES 20-25

The amphetamine led to a highly significant between group and repeated measures effect at minutes 20-25, as illustrated by Table 28 and Figure 19 (Note: Because the groups showed nonsignificant differences between them on the presurgery activity measure, the analysis was rerun, comparing amphetamine affected activity at weeks 2, 6, 10, and 14, using presurgery activity levels as a covariate. The results were the same; i.e. F (between group)= 12.830; 2, 16 df; $p<.001$). Between group comparisons revealed that both the implanted group ($t=3.67$; $p<.01$) and lesioned only groups ($q=5.77$; $p<.01$) were more active than controls.

Despite the repeated measures effect ($p<.001$), within group comparisons revealed that no group showed a significantly increased hyperactivity past that evidenced at week 2 postimplantation. Thus there was not an increased hyperactivty (i.e. a progressive motor dysfunctioning) during minutes 20-25 over the course of the experiment.

(iii) MINUTES 55-60

As with the effect at minutes 20-25, the amphetamine caused a significant between group difference at minute 55-60 postinjection

TABLE 27: MINUTES 5-10 POST AMPHETAMINE INJECTION: # OF SQUARES CROSSED

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	135349.38	2	67674.693	1.539	.242
ERROR	747521.31	17	43971.842		
WITHIN SUBJECTS (REPEATED MEASURES)					
WEEKS	414433.56	4	103608.391	9.967	.001
LESION X WEEKS	80311.410	8	10038.926	.966	
ERROR	706880.42	68	10395.300		

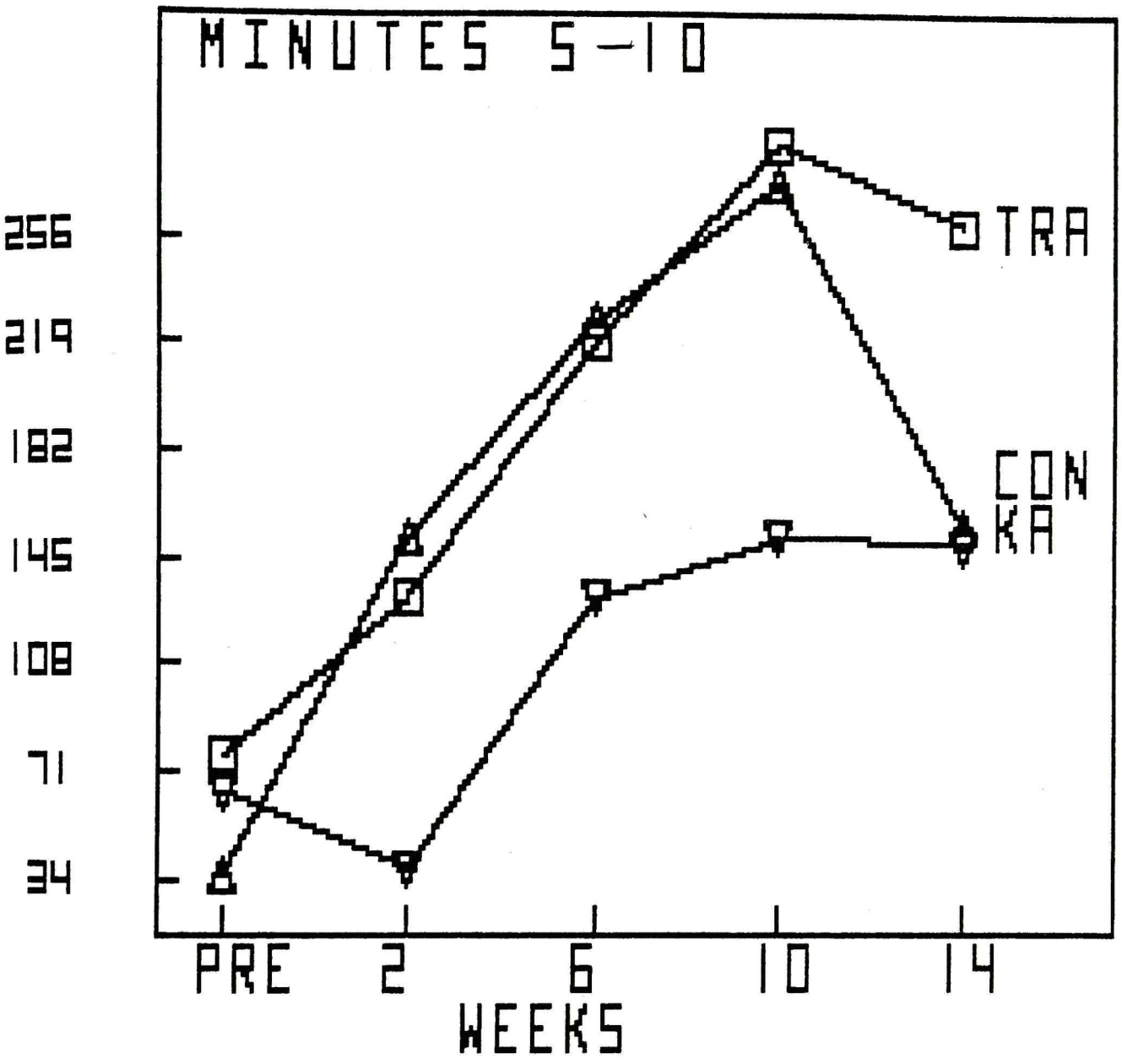


FIGURE 18: Mean number of squares crossed during minutes 5-10 after amphetamine administration. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls.

TABLE 28: MINUTES 20-25 POST AMPHETAMINE INJECTION: # OF SQUARES CROSSED

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	554400.005	2	277200.002	8.464	.003
ERROR	556747.012	17	32749.824		
WITHIN SUBJECTS					
WEEKS	277234.722	4	69308.680	6.969	.001
LESION X WEEKS	80297.616	8	10037.202	1.009	.430
ERROR	676318.120	68	9945.855		

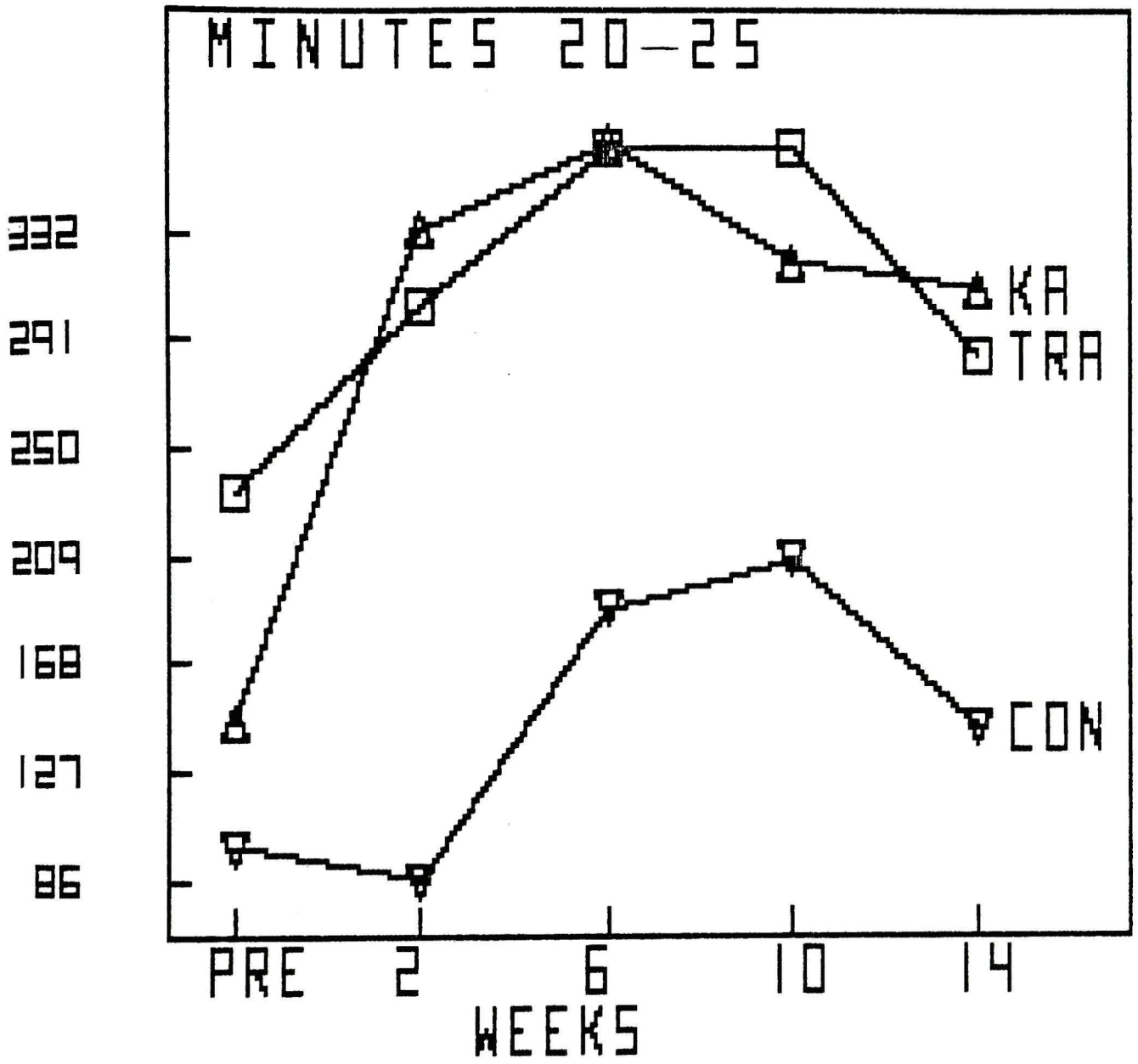


FIGURE 19: Mean number of squares crossed during minutes 20-25 after amphetamine injection. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls.

TABLE 29: MINUTES 55-60 POST AMPHETAMINE INJECTION: # OF SQUARES CROSSED

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	428165.97	2	214082.99	9.071	.002
ERROR	401205.49	17	23600.32		
WITHIN SUBJECTS					
WEEKS	104830.07	4	26207.52	2.471	.052
LESION X WEEKS	72079.65	8	9009.96	.849	
ERROR	721334.65	68	10607.86		

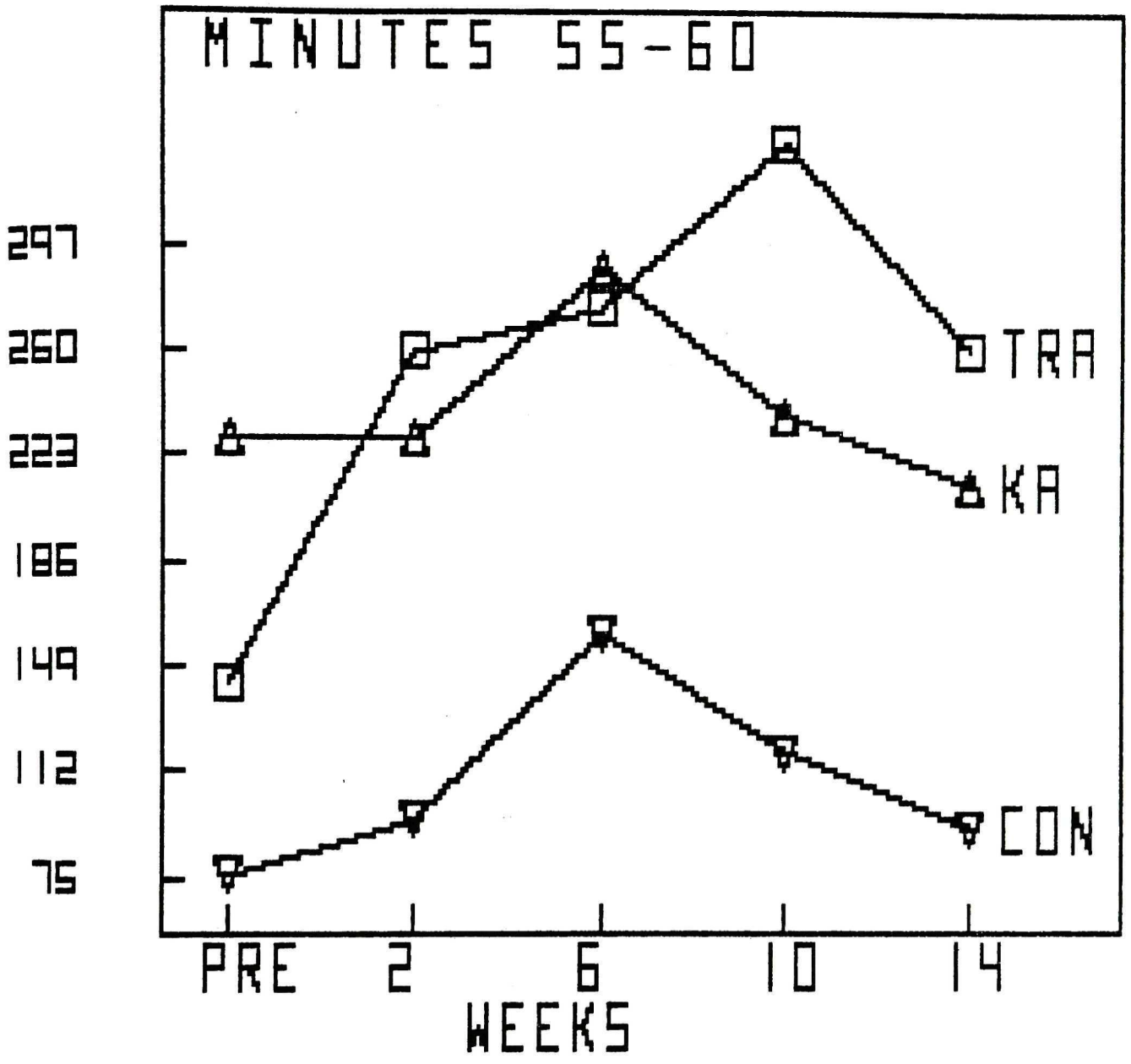


FIGURE 20: Mean number of squares crossed during minutes 55-60 post amphetamine injection. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls.

(p=.002. Note: as the large nonsignificant presurgery differences were felt to be capable of contributing to the between group effect, the analysis was rerun in order to control for this variation. This is shown in Table 29 and Figure 20. When presurgery activity levels were used as a covariate for the analysis, the results were the same; i.e. F (between group) = 10.075; 2,16 df; p=.001). Between group comparisons revealed that both the implanted group (t=3.82, p<.01) and lesioned only groups (q=5.05; p<.01) were significantly more active than controls. Within group comparisons revealed that at no time did any group "deteriorate" after the week 2 measure; i.e. no significant increase in activity within any group was noted after the 2 week measure.

(3) REARS

The number of times animals reared during the first 5 minutes on the open field were compared accross the five different test sessions; i.e., prior to surgery, 2 weeks, 6 weeks, 10 weeks, and 14 weeks postimplantation. A similar analysis was done for rears seen at minutes 55-60, and at minutes 5-10, 20-25, and 55-60 post amphetamine injection. There were no significant between group or interaction effects at any time, on any of the measures.

(4) SUMMARY OF OPEN FIELD RESULTS

In summary, the implanted group was significantly more active than controls during the first 5 minutes they were in the field, and at minutes 20-25 and 55-60 post amphetamine injection. The lesioned only

group was significantly different from the control group only at minutes 20-25 and 55-60 post amphetamine. There was no evidence of a progressive motor deficit after the kainic acid lesions. That is, the lesioned animals did not become more hyperactive during the course of the experiment. There were no significant differences of any kind found on the rearing behavior.

(f) METRAZOL CONVULSANT

After completion of the T-maze running at 14 weeks postimplantation, rats were given 3 days of ad lib feeding, and then received a subcutaneous dose of 70 mg/kg metrazol, according to the methodology of Pisa, Sanberg, Corcoran, and Fibiger (1980). Since not all animals survive this challenge, two implanted and two lesioned only animals did not undergo injection in order to keep them alive for the immunocytochemistry perfusion. Thus a total of 16 animals underwent metrazol injection.

Over the next 20 minutes, three measures were obtained, including latency to the first ictal response and the first grand mal seizure, and total duration of the first grand mal. As in experiment one, the first obvious abnormal response was a pronounced myoclonic jerk. Characteristically, the animals would forcefully retract their head, extend their forepaws, and contract their musculature. There was a great deal of variation as to when this pre-ictal resonse was observed in the implanted and control groups, with the range extending from 63 to 668 seconds in the implanted group, and 75 to 1155 seconds in the controls. Conversely, there was relatively little variance in the lesioned only group, with all animals showing the first ictal response

between 115 and 280 seconds postinjection. There were no statistically significant between group differences. The results from the statistical analyses done on this measure are shown in Appendix H.

(g) HISTOLOGY

At the time of sacrifice, four implanted, five lesioned only, and six controls were injected with chloropent anesthesia and transcardially perfused with phosphate buffered saline (ph 7.4), followed by a 10% solution of formalin/PBS. The remaining animals underwent glutaraldehyde perfusion for tyrosine hydroxylase (TH) immunocytochemistry. The TH immunocytochemistry was done in an attempt to evaluate if the transplants were able to induce ingrowth of dopaminergic (presumable from the substantia nigra) fibers, as exists in the endogenous striatum.

Cell counts from seven regions of the brain, as defined by the atlas of Konig and Klippel (1967) were made by counting five high power cell fields (1000x) per area, averaging them, and analyzing the between group cell counts via the use of one-way ANOVAS. A priori contrasts were done between the lesioned only vs implanted groups, and the control vs implanted groups, when significance was obtained. A posteriori contrasts were done on the lesioned only vs control comparisons at these times.

The mean cell counts, and standard deviations, for each region of the brain are presented in Table 30. As can be seen, there were significant between group differences for the three striatal regions, but not for the pyriform cortex, amygdala, hippocampus, or VMH regions.

but not for the pyriform cortex, amygdala, hippocampus, or VMH regions. Light microscopy revealed detectable extra-striatal degeneration in 2 brains. Specifically, a discrete region of field CA3a of the hippocampus, as well as field CA4, was clearly lesioned in one implanted, and one lesioned only animal at the level examined. Thus, in these 2 brains, there was evidence of disturbances of the neurons at least in the hippocampus that was not reflected by the cell counts.

TABLE 30: CELL COUNTS

	mean	sd	mean	sd	mean	sd	F	p
	implant		lesioned		controls			
STRIATUM								
8920	15.8	3.81	3.6	1.9	27.7	9.3	23.6 (2,15)	<.01
8280	21.4	6.8	4.7	1.8	28.5	5.5	36.5 (2,15)	<.01
7890	18.3	3.5	10.0	5.5	23.8	6.2	10.9 (2,15)	<.01
PYRIFORM								
8280	50.5	13.1	38.7	17.4	52.2	13.1	1.5 (2,15)	NS
AMYGDALA								
7020	16.1	6.4	13.2	3.4	21.2	6.7	3.3 (2,15)	NS
HIPPOCAMPUS								
3930	19.7	.93	22.4	6.9	27.4	4.7	3.3 (2,13)	NS
VMH								
4230	45.1	5.4	39.2	20.4	67	33.9	1.9 (2,13)	NS

All three regions of the kainic acid lesioned striatum showed a significant decrease in the neuronal population compared to controls, both in regions 8920 ($q=9.7$; $p<.001$) and 8280 ($q=11.9$; $p<.001$). A somewhat increased number of neurons was, however, noted in the most caudal striatal region (7890, $q=6.6$; $p<.01$).

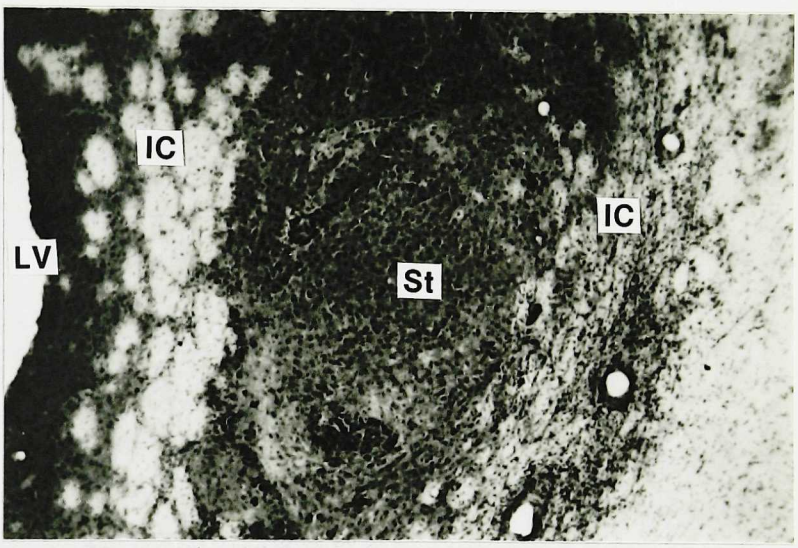
Eleven of the 12 transplants deposited within the striatum grew robustly (Photo 1), ranging in size from 700 um--4900 um in an anterior/posterior direction.

Planned comparisons done on the cell counts revealed the transplanted rats to have significantly more striatal neurons than the lesioned only group in regions A 8920 and A 8280. Conversely, transplanted rats had statistically fewer neurons than controls in region A 8920. Post hoc comparisons revealed the lesioned only group to have fewer neurons than controls at all levels of the striatum.

Although occasional small patches of necrosis were seen in half of the transplants deposited within the striatum, they occupied less than 10% of the transplanted area, and most frequently occured in the vicinity of the corpus callosum (CC). When present, the necrosis appeared as small, oval, opaque crystalline patches that poorly took the Nissl stain, and were accompanied by occasional macrophages.

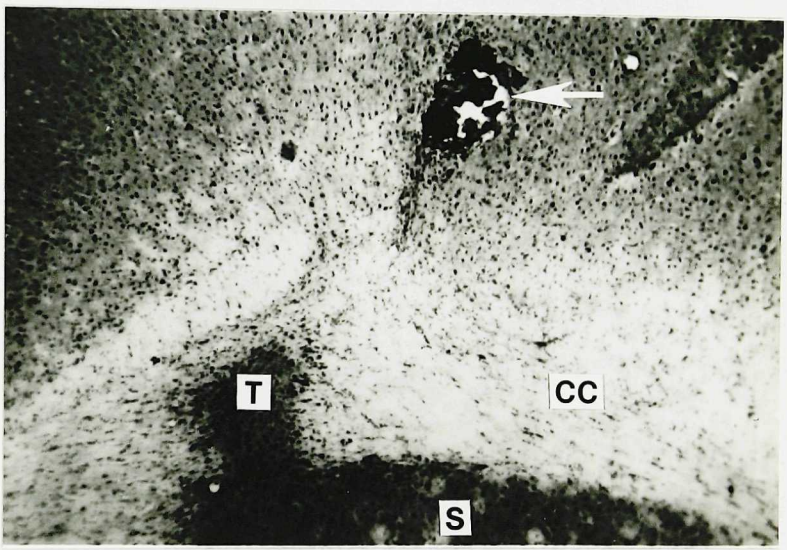
As the transplanted fetal striatum passed through the CC, a gliosis occurred, at times so intense as to make visualization of the CC difficult (Photo 3). The CC appeared to act as a boundry, above which the transplants perished, below which they survived well. This suggests that the CC may serve in the intact brain as a physical barrier that biochemically isolates the striatum from the overlying neocortex, and protects the developing striatum from toxic effects of the cortex. As it passed out of the CC and into the neocortex, the transplant, which

PHOTO ONE



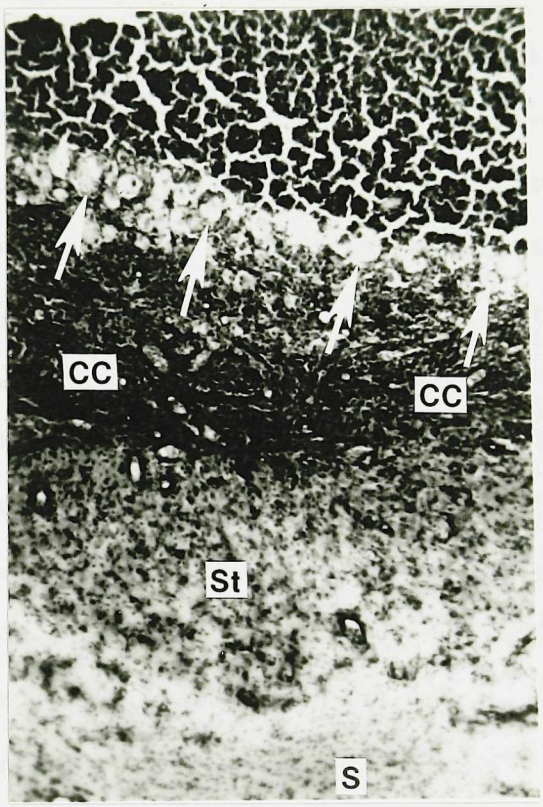
Intrastriatal transplant (St) within the lesioned host striatum, pushing fibers of passage (IC) laterally out to the corpus callosum and medially towards the lateral ventricle (LV). Brain sections were cut at 30 um in the coronal plane, stained with 0.1% cresyl violet, and photographed at approximately 300x.

PHOTO TWO



Striatal transplant (T) survives both within the host striatum (S) and corpus callosum (CC), but degenerates as it emerges dorsal to the corpus callosum and into the neocortex (arrow). Brain sections were cut at 30 um in the coronal plane, stained with 0.1% cresyl violet, and photographed at approximately 300x.

PHOTO THREE

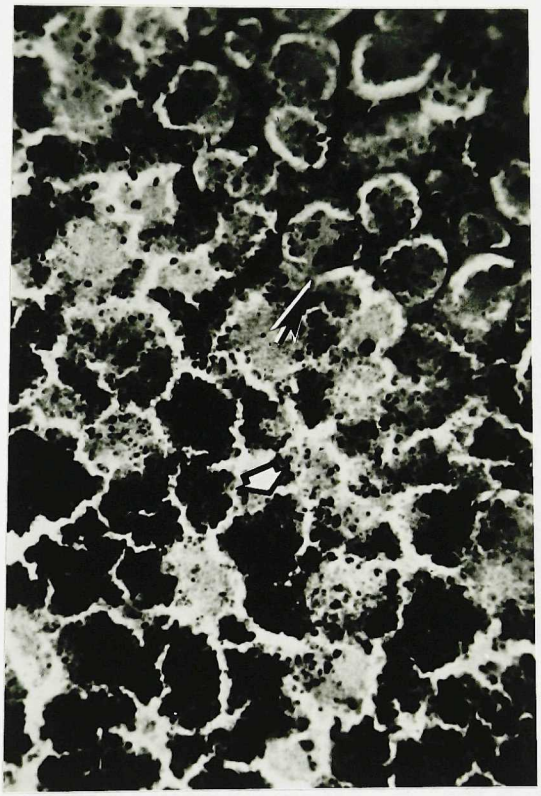


Intense gliosis of the corpus callosum (CC) bordered ventrally by fetal striatal transplant (St) and lesioned host striatum (S), and dorsally by a ring of degenerating neurons (arrows) surrounding an area of complete necrosis. Magnification is approximately 300x.

had survived robustly only a few hundred microns ventrally, degenerated extensively in 11 out of 12 rats (This effect was noted in 2 of the 4 transplants sacrificed at week 3 in the pilot study. The intact 3 week transplants showed robust growth along the entire ventral/rostral gradient, from the striatum to the surface of the neocortex). Of the 11 degenerated neocortical grafts examined at 4 months, 10 showed evidence of a progressive degeneration that was still active at the time of sacrifice. In the middle regions of these grafts were large areas of basophilic necrotic tissue that appeared to be loosely clumped chromatin (Photo 4). No identifiable neurons, glial cells, or other well formed cellular material, and no signs of inflamation (i.e. lymphocytes, red blood cells, etc.) were seen in this region. As in the intrastriatal grafts, however, small, oval, opaque crystalline patches of necrotic tissue accompanied by macrophages were often found scattered throughout regions of the cortically deposited transplants (Photo 2). The necrotic transplants were located immediately dorsal to the successfully implanted striatum, in an identical location to the surviving 3 week neocortically deposited grafts. Surrounding the outermost borders of the necrotic tissue was a ring of swollen neurons, from one to several cells deep, undergoing chromatolysis (Photos 3 and 4). These cells appeared to be the source of the chromatin previously mentioned.

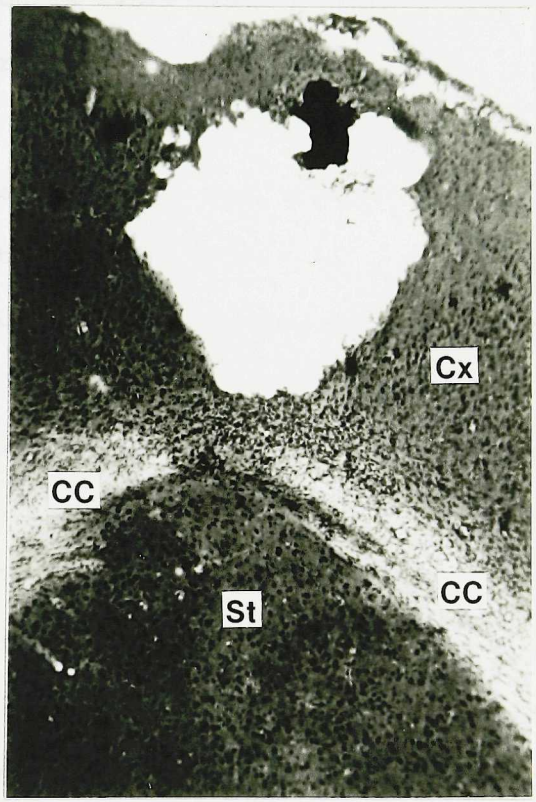
Two cortically deposited transplants sacrificed at 4 months did not fit the above description. One was devoid of all tissue, and consisted of an oval, empty space immediately above the successfully transplanted striatum (Photo 5). The other consisted of a poorly surviving transplant, occupying approximately one-third of the transplanted cortical area, with few neurons, many glial cells, and many necrotic patches. Sham implanted controls evidenced only a small glial

PHOTO FOUR



High magnification (500x) of swollen, ectopic cell bodies of degenerating neurons (dark arrows) undergoing eventual chromatolysis (light arrow).

PHOTO FIVE



Striatal implant (St) within the host striatum bordered dorsally by the corpus callosum (CC) and the dilated cavity of the cortically (Cx) deposited transplant. Magnification approximately 300x.

scarring of the capillary needle tract, and none of the other changes described in the implanted group.

It is unlikely that immunological rejection accounted for the degeneration in the cortically deposited striatal tissue, since the entire transplant was not killed. Others have noted that when rats are preimmunized so as to reject allogenic tumor cells transplanted into the brain, the rejection is rapid (Raju & Grogan, 1977) and characterized by necrotic areas surrounded by clusters of lymphocytes (Lodin, Hasek, Jitka, Sladecek, & Holan, 1977). The destruction of the cortically deposited grafts was characterized by a slow process of degeneration that was partial at 3 weeks and complete at 4 months, and appeared to destroy all transplanted cells without the presence of lymphocytes. This suggests that the neocortex, but not striatum, of the adult recipients was slowly toxic to the striatal grafts, and accounted for the degeneration noted.

One explantation for the apparant toxicity of the neocortex to the fetal striatum is that pools of available glutamate may be greater in the neocortex than in the striatum. It is known that kainic acid, a rigid analog of glutamic acid, loses its neurotoxic potential if cortical glutamatergic projections to the striatum are severed prior to injection (Bizziere & Coyle, 1978; McGeer, McGeer, & Singh,1978). Similarly, chronic infusions of glutamate directly into the striatum lead to pathological changes similar to those produced by kainic acid (McBean & Roberts, 1984). It is possible that higher pools of glutamate exist in the neocortex and lead to the increased necrosis seen in the striatal grafts. This explanation would account for the neuronal degeneration noted, but does not explain the degeneration of the glial cells that were transplanted along with the neurons.

In keeping with previous reports (Kimura et al., 1980; Schmidt et al., 1981), this experiment found that transplants of fetal striatum grew in the lesioned adult host striatum. The results suggest that the neocortex is toxic to the striatum. Previous work has indicated that the rat neocortex is capable of supporting growth of fetal neocortex (Dunn, 1917; Labbe et al., 1983; Legros Clark, 1940), substantia nigra (Bjorklund & Stenevi, 1979), and cerebellum (Das, 1975; Labbe et al., 1983). It is believed that this is the first report of the adult rodent neocortex being unable to support growth of intraparechymal fetal brain transplants.

Unfortunately, the TH immunocytochemistry, which was intended to evaluate if TH positive fibers invaded the transplant, did not work well. This method is still under developement in the laboratory where they were done (D. Price, Johns Hopkins Hospital), and most probably two aspects of the procedure, including a poor perfusion, and use of the cryostat (instead of vibrotome) accounted for the poor results. The antibody reacted group stained with no more apparent intensity than did its non-reacted control in any of the animals, including controls. Background staining was particularly intense, apparantly due to the presence of RBC's, and appeared to account for the large background noise and poor results.

In summary, the striatum in the lesioned only group was significantly depleted of neurons. The implanted group had significantly greater cell counts in all three striatal regions, but did not have as many neurons as did the control group. The transplants survived well in the striatum, but did not seem able to survive dorsal to the CC into the neocortex.

(vi) DISCUSSION

(a) SPONTANEOUS ANIMAL ACTIVITY

Experiment one replicated work by others which found that for up to 3 weeks after kainic acid lesions of the striatum in male Wistar rats, there was no difference in general daytime locomotor activity or rearing behavior (Dunnett & Iversen, 1981; Mason et al., 1978a; 1978b; Sanberg, Pisa, & Fibiger, 1978). Unlike the findings in the male rats, in experiment two locomotor deficits were produced in the lesioned rats. The lesioned female Sprague-Dawley rats were statistically hyperactive compared to controls on several measures, including movement time, horizontal activity, stereotypical time, and number of stereotypical movements. Obviously, it is possible that either the strain, sex, or an interaction effect of these two variables led to the hyperactivity in the females. This finding suggests, but certainly does not prove, that the striatum of female Sprague-Dawley rats is involved in the "tonic" regulation of movement.

An alternative explanation from the one listed above is that the cause of the locomotor abnormalities is a progressive deterioration of the animal over time. The finding in this experiment of increased hyperactivity 12 weeks after lesioning in females (but not at 2 weeks in the male Wistars in experiment one) might represent such a progressive deficit.

To better understand the causes of this hyperactivity, a third experiment comparing locomotor activity of male Wistars, male Sprague-Dawleys, and female Sprague-Dawleys between 3 and 12 weeks after kainic acid lesions will need to be done. This will allow for a more

complete assessment of possible sex and strain differences regarding striatal regulation of locomotion.

The implanted animals were not identical to controls. They evidenced a hyperactivity during the first 10 minutes in the monitor on total distance and number of stereotypical movements. Additionally, they moved significantly more often than controls on number of stereotypical movements for much of the first half of their time in the monitor. Despite these persisting deficits in the implanted animals, they were not as impaired as the lesioned only group. Implanted animals had a statistically significant recovery on horizontal activity, stereotypy time, and movement time. In addition, the implanted animals, although evidencing more stereotypical movements than controls, showed these movements in a different way than the lesioned only group, moving quicker and more often than lesioned only group on this behavior. Thus the implants led to a partial recovery of the locomotor deficits caused by the kainic acid lesions, and led to a pattern of locomotor behavior on stereotypy that was different both from the control and lesioned groups.

This result futher suggests that the striatum in female Sprague-Dawley rats is involved in the "tonic" regulation of locomotion. Both removal of striatal tissue with kainic acid lesions, and replacement of this lost tissue with striatal grafts, appears to affect the spontaneous locomotion of the rats.

(b) NEUROLOGICAL EXAM

The neurolgical exam was included in this experiment because others (Dunnett & Iversen, 1981) had found it to provide useful

information about sensorimotor functioning in rats. It was felt to offer new information regarding behavioral effects of striatal kainate lesions not presently available.

Persistent and enduring deficits beginning after the kainic acid lesions were found in both the lesioned only and implanted groups compared to controls. These results suggest that kainic acid lesions of the striatum in rats lead to an inability on the part of the rat to orient to various kinds of peripheral stimuli. The deficit could be the result of a number of different problems, including (1) decreased proprioception/nociception, (2) decreased arousal/attention, and (3) decreased ability to skillfully move in order to orient towards or away from a stimulus. The first two deficits, decreased proprioception/nociception and arousal/attention, are unlikely. All three groups reacted to the noxious measures with distressed vocalizations. Thus they perceived the (noxious) stimulus, and seemed to react to it in similar ways. The deficit is more likely to be either decreased ability in the rat to spatially detect where the noxious stimulus is, or decreased ability to skillfully move (i.e. an apraxic deficit). Such a deficit would prevent the animals from skillfully coordinating various muscular movements, and would interfere with their ability to orient towards or away from the stimulus. Previously, it had been reported that rats with kainic acid lesions suffer from an apraxia (i.e., a deficit in skilled movement) for several days after kainic acid surgery. They cannot handle or chew food pellets well (Sanberg & Fibiger, 1981). Similarly, I have previously noted that they literally cannot locate their drinking tube with their paws or mouth, although they will drink voraciously if the straw is placed against their lips. These effects wane after several days. As the rats suffer from a clear

apraxic (i.e., decreased ability to move skillfully) deficit early after lesioning, it is likely that the results found on the total neurological score are at least partially a representation of a continuing apraxic deficit. Thus the striatal lesions appeared to affect the long-term ability of the rats to successfully respond on the neurological exam.

The implants had no effect on this behavioral deficit. At no time were implanted animals statistically different from lesioned only animals. Thus, while the lesions suggest that the striatum is involved in skilled movements, replacing the lost tissue did not restore the behavioral deficit, most probably due to limitations (i.e., incorrect anatomical integration, insufficient amount of fetal tissue, etc.) of the transplantation methodology.

(c) T-MAZE RESULTS

It has previously been reported that kainic acid lesions of the striatum lead to large and persistent deficits on a rewarded alternation T-maze task in male rats of the Wistar and CYF strain (Divac et al., 1978; Dunnett & Iversen, 1981; Pisa et al., 1978). The current experiment broadened that finding by demonstrating this deficit to occur in female rats of the Sprague-Dawley strain.

In addition, this experiment found that part of the nature of the T-maze deficit is due to an increased number of same sided alternations (i.e. perseverations) by the lesioned animal. The perseverative responses might be secondary to ancillary frontal lobe involvement, as this type of damaged has been implicated in such behavior (Schwob, Fuller, Price, & Olney, 1980). Irregardless of the etiology, the female Sprague-Dawley rats showed clear evidence of a complex behavioral

deficit, performing poorer than controls generally while emitting more perseverations. Thus the behavioral deficits that occur on complex tasks after kainic acid lesions of the striatum occurred across sex and strain, and suggest that the striatum has a role in regulating this behavior.

Two sets of investigators have examined the ability of neural implants to influence rewarded alternation deficits. Most recently, Labbe et al. (1983) found that fetal frontal implants reversed an alternation deficit in water deprived rats following bilateral suction aspirations of the frontal cortex. The lesioned only group, as well as an additional group that received cerebellar implants, did not recover. Despite improvement over the lesioned only group, frontally implanted animals continued to do significantly worse than controls. Of particular interest is that Labbe's group found that recovery on the T-maze occurred between 2-4 weeks after implantation. As this is not a sufficient amount of time to pass for the implants to reinnervate target tissue, Labbe et al. (1983) concluded that the functional recovery might be due to nonspecific neuronotrophic substances, such as specific nerve growth factors.

Additionally, Dunnett et al. (1982) assessed food rewarded T-maze behavior in rats that received fimbria/fornix transections followed by bilateral solid septal grafts, bilateral septal suspensions, bilateral locus coeruleus grafts, or no grafts. They reassessed these animals for 8 weeks of training beginning 7 months after the implantation. Although the implanted animals were still significantly impaired on the T-maze compared to controls, both types of septal grafts significantly reversed the deficit. The lesioned only group, and locus coeruleus group, alternated at a 50-60% level throughout their postsurgery retraining.

Although partially reversing the T-maze deficit, the septal grafts did not ameliorate the lesion induced disturbances in spontaneous activity or spontaneous alternation.

That the implanted group recovered on rewarded alternation also strongly suggests that the striatum is involved in regulating the behaviors that lead to successful T-maze performance. This finding conceptually replicates the work by Labbe et al. (1983) and Dunnett et al. (1982) in a different brain region. As with the frontal and fimbria/fornix implants, fetal striatal implants partially reversed a T-maze deficit following lesioning of the host striatum. Dunnett et al. (1982) found that seven of nine rats with solid septal grafts, and four of five with septal suspensions, acquired the task by week 8 at control levels, whereas the remaining three rats in the two groups remained at chance level. Only two of the six implanted animals in the current experiment showed evidence of returning back to control levels, with the remaining four performing between the lesioned only and control levels. The partial recovery in the implanted group may be a reflection of the relatively brief retraining the animals were given postimplantation, compared to the 8 weeks of retraining that Dunnett's group did. Alternatively, it may be that partial instead of full recovery occurred because of distant lesions caused by the kainic acid. Specifically, cell loss in region CA3a, and CA4 of the hippocampus, was grossly noted in two animals, and may have existed to a less obvious degree in the others. It has previously been reported that kainic acid lesions of this region of the brain lead to severe deficits in T-maze performance (Deckel, Grunberg, & Sarvey, 1982; Handelman & Olton, 1981). Thus the partial recovery of the implanted group may have resulted because only the striatum, and not the striatum and hippocampus, were replaced.

Further experimentation will be required to assess the contribution of the hippocampal lesions to the enduring T-maze deficits found in the implanted group.

Based on the findings of Labbe et al. (1983), it will be important in future experimentation to assess how quickly after grafting the implanted group shows evidence of recovery. Labbe's finding of recovery before the grafts were able to make synaptic contacts suggests that nonspecific aspects of the graft accounted for the recovery. Neither this experiment, nor the work of Dunnett et al. (1982), assessed this issue. In order for the physiological mechanisms of postimplantation recovery to be understood, it will be important to determine if nonspecific effects are accounting for the recovery seen in numerous different behaviors in implants in different regions of the neuraxis.

In summary, these results suggest that the striatum is involved in mediating the processes (i.e., attention, memory, motivation, etc.) that are required in T-maze performance. The finding of partial recovery in T-maze behavior following kainic acid lesions of the striatum extends the implantation literature, and points to additional experiments that will be required to further assess the contribution of specific factors of the implant in reversing the deficit.

(d) BODY WEIGHT DIFFERENCES

(1) LESIONED ANIMALS

Experiment one replicated earlier work in finding that the kainic acid lesions in male Wistar rats leads to a temporary adipsia, aphagia,

and body weight reduction for the 2 weeks after lesioning (Divac et al., 1979; Pettibone et al., 1978; Sanberg & Fibiger, 1979; Sanberg, Lehmann, & Fibiger, 1978a; Sanberg et al., 1979a). Unlike the male Wistar rats, the female Sprague-Dawley controls (which weighed on the average 1 gram more than the lesioned only group, and 7 grams more than the implanted group on the day of surgery) weighed 32 grams less than the lesioned only group, and 23 grams less than the implanted group, by 14 days after lesioning. This weight difference gradually increased, until the lesioned only group weighed on the average 48 grams more than controls by the end of the experiment. This finding has no precedent that I know of in the literature. Although it is possible that the effect was caused by the use of Sprague-Dawley rats, this is highly unlikely. Male rats of a variety of strains, including Wistars (Divac et al., 1978; Pisa, Sanberg, & Fibiger, 1980; Sanberg, Lehmann, & Fibiger, 1978; Sanberg, Pisa, & Fibiger, 1979), CYF (Dunnett & Iverson, 1981), Woodlyn (Mason et al., 1978b; Mason & Fibiger, 1979), and Long Evans hooded (R. Smeyne, personal communication, November 21, 1984) all show no weight changes in the direction found in the female Sprague-Dawleys. Further, workers using chronic preparations of male Sprague-Dawleys, although not systematically examing weight changes, report no obvious between group differences in male lesioned vs control animals several months after the lesions were made (R. Zaczek, personal communication, December 14, 1984). Thus it is likely that the increased weight seen after kainic acid lesions in the female Sprague-Dawley rats is a function of the sex, and not strain, differences. This conclusion will of course need to be experimentally verified. It suggests that there exists a different type of neural control over feeding in the female rat compared to the male. Whereas the male rat has a permanent loss of body weight after the

lesioning, the female rat has a permanent gain. Although males have a weight loss 14 days after the kainic acid lesions (Sanberg & Pisa, 1979; experiment one), the females showed a gain of 27 grams over controls during the same time span.

(2) WEIGHT DIFFERENCES IN THE IMPLANTED GROUP

The implanted group showed a nonsignificant increase in weight over the lesioned only group beginning at week 6 after implantation, and continued in their rate of gain through week 8. From that time, the implanted group maintained a rate of weight gain parallel to the other two groups. It should be noted that the implanted group was not significantly different from the lesioned only group, and that the effect of the lesion, and not transplant, could possibly account for the weight gain in the implanted group. Obviously, future experimentation will be required, first to verify/clarify the effect, and then more carefully explore it.

To explain the weight findings, it could be postulated that the lesions and/or the implants distantly affected the VMH region of the hypothalamus. Kainic acid does cause widespread lesions throughout the neuraxis when injected into the brain, and can cause hypothalamic lesions (Olney, Sharpe, & DeGubareff, 1975). Several aspects of the experiment argue against this being the explanation of the weight gain, however. First, cell counts of VMH revealed no significant between group differences, indicating that there was no obvious damage of this region. Second, the pattern of weight gain is radically different from that seen in hypothalamically lesioned animals. Female and male rats with VMH lesions gain approximately 60 grams the first 2 weeks after

lesioning (Teitelbaum, 1955; Teitelbaum & Campbell, 1958), eventually showing weight gains of 200 grams or more over controls 3 months later. The same pattern of weight gain is seen in rats with parasagittal knife cuts that separate the medial from the lateral hypothalamic areas (Paxinos & Bindra, 1972). Twelve weeks after lesions were made in this experiment, lesioned animals were only approximately 50 grams heavier than controls, while implanted animals were only 80 grams heavier than controls. Thus the rate of gain was far slower than what would be expected in animals with VMH lesions. It is possible that the rate of gain was slower only because the distant lesions from the kainic acid were very small and subtle. This possibility cannot be ruled out in this experiment, but is unlikely, as the male rats in experiment one, which had identical lesions, showed a very different response to the surgery. Thus, the pattern of weight gain, the sex specificity of it, and the lack of obvious VMH damage, all argue against a VMH hypothalamic etiology of the weight gain.

It is possible that the weight changes are from distal LH hypothalamic lesions, or lesions of the dopaminergic nigrostriatal bundle (NSB). Previous work has shown that both these lesions cause a temporary aphagia and adipsia, and decrease body weight in comparison to controls (Blundell & Lesham, 1974; Levine & Schwartzbaum, 1973; Pettibone et al., 1978; Sanberg & Pisa, 1979). It has previously been shown that rats recovered from either NSB or LH lesions display a type of drinking behavior called "prandial drinking" (Levine & Schwartzbaum, 1973; Sanberg & Pisa, 1979; Teitelbaum & Epstein, 1962). These rats consume water primarily to wet their mouths, and markedly reduce fluid intake when food is removed. Thus the hyperadipsia they display is seen only under conditions where free access to food exists. In this

experiment, a different type of drinking behavior was found. First, a hyperadipsia was found during ad lib feeding. Secondly, the relative extent of this hyperadipsia remained constant across both food deprived, and ad lib feeding conditions. Thus the hyperdipsia seen in the lesioned rats was not dependent on food consumption, as is the hyperadipsia in LH/NSB rats. This replicates the finding by Sanberg and Fibiger (1979), who likewise found that kainic acid lesions cause a "non-prandial" hyperadipsia.

Taken together, these findings replicate earlier work in implicating the striatum in the regulation of body weight in rats. However, in contradistinction to findings in the male rats, these results suggest that there is a sex difference in the striatum's role. Specifically, this experiment suggests that female Sprague-Dawley rats increase their body weight after kainate striatal lesions. While others have commented on the ability of striatal lesions to decrease the rate of weight gain in male rats, this is the first report that indicates a different type of response in females. It does not appear that the weight gains in the implanted group was due to distant lesions, as the behavioral parallels to animals with these lesions do not fit. Rather, it may be that female rats have a different neural organization of feeding than male rats, that the striatum is intricately involved in this circuit, and that its role in modulating weight is different from that seen in the VMH or LH region of the hypothalamus.

(3) AD LIB AND INSULIN AFFECTED EATING AND DRINKING

Previously, Sanberg and Fibiger (1979) reported that male Wistar

rats with kainic acid lesions exhibit a nonsignificant tendency to consume more ad lib food and water per gram body weight than do controls. This experiment replicates that finding. Rats with kainic acid lesions ate more food than controls for the 24 hours prior to, during, and after insulin injection. Similarly, the lesioned group drank more than controls for the same three 24 hour feeding periods. Like Sanberg and Fibiger's findings, these results were not statistically significant. Nonetheless, the trend by the group with kainic acid lesions to eat more than controls per gram of body weight suggests that one contributing factor to their weight gain is increased food consumption.

The implanted animals likewise showed a nonsignificant trend of eating more than controls, consuming similar amounts of food per gram of body weight as the lesioned group. In addition, the implanted animals drank significantly more than controls, and showed a trend towards drinking more than lesioned only animals. It is unlikely that the increased fluid consumption accounted for the increased weight gain in the implanted group over the lesioned group. Increased hydration is not capable by and of itself of causing the greater fat deposits noted in these animals on postmortem examination. Thus the mechanism by which the weight gain between these two groups can be understood is not elucidated by examination of ad lib feeding.

The insulin injections were done in an attempt to assess if the weight gains in the implant/lesion groups resulted from changes in number or sensitivity of glucoreceptor/insulin receptors. Based on the work of Ritter et al. (1978), it was hypothesized that if these receptors had been altered by the experimental manipulation, changes in eating behavior following insulin administration would be seen between

groups. However, the insulin manipulation led to no between group differences. Based on these findings, there is no evidence to suggest that there are central differences in glucose or insulin receptors following kainic acid lesions and/or implantation of fetal striatal tissue.

(4) FOOD DEPRIVATION

During the 24 hours that all animals were deprived of food, controls lost significantly more weight per gram of body weight than either the lesioned or implanted group. Additionally, the lesioned group showed a nonsignificant trend to lose more weight than implanted animals. These results suggest that the groups may have been different metabolically in the starved state. Both the lesioned and implanted group apparently catabolized less body fat than controls. While it is possible that these two groups moved less than controls in the starved state, and thus "burned off" less, it is unlikely. This experiment demonstrated that, when placed in a novel setting, the lesioned and implanted groups moved more often than controls. Similarly, Mason and Fibiger (1979) found that rats with kainic acid lesions showed increased activity at night compared to controls. Thus, if any changes in locomotion occurred, they most probably were in the direction of increased rather than decreased movements in the group with the kainic acid lesions.

When animals were allowed to eat again following food deprivation, the lesioned only group ate significantly more than the implanted groups for the 24 hours, but not the first hour, after deprivation ended. They were nonsignificantly different from controls.

This replicates the finding by Sanberg and Fibiger (1979) who reported that male Wistars similarly consumed more food than controls at the end of 24 hours of starvation. While the neurobiology of the increased eating after the food deprivation is unknown, nonetheless this finding points to a qualitative difference between the implanted and the lesioned only group.

(5) SUMMARY OF WEIGHT FINDINGS

The female Sprague-Dawley rats with kainic acid lesions of the striatum parallel the male rats in their eating behavior in several ways. Like the male rats, they had a nonsignificant tendency to drink more than controls, both under ad lib feeding, and after being food deprived. Additionally, they ate more than controls both during food deprivation, and during ad lib feeding. They differ from the males in their increase, as opposed to decreased, weight gain over time.

The implanted group was qualitatively different from the lesioned only group in that they ate less than the lesioned group during the 24 hours after food deprivation ended. Otherwise, they were nonsignificantly different in all other food/weight related measures.

(e) OPEN FIELD

The lesioned only group of female Sprague-Dawley rats became significantly hyperactive compared to controls in response to amphetamine injection at minutes 20-25 and minutes 55-60, showed a

nonsignificant trend towards hyperactivity at minutes 5-10, and were not different from controls at minutes 0-5. This replicates work by others (Fibiger, 1978; Mason et al., 1978a; 1978b; Sanberg, Pisa, & Fibiger, 1979a; 1979b) as well as the finding in experiment one. It extends this earlier work by finding that the amphetamine induced hyperactivity occurred in rats of a different strain, and different sex. Furthermore, this effect was found using squares crossed in an open field, as opposed to photocell beam interruptions in an electronic monitor. Thus the effect is a robust one, and extends across sex, strain, and variations in the behavioral measures. The findings here reported on horizontal activity strengthen the robustness of the model by extending earlier work in male Wistar rats to female Sprague-Dawley rats.

In experiment one, it was found that the hyperactivity caused by the amphetamine was seen only in the horizontal plane. This result is replicated here. The female rats increased the squares crossed, but not the number of rears, after amphetamine injections. Thus the striatum of the female Sprague-Dawley rats, like the striatum in male Wistars, appears to have a dopaminergic modulation of horizontal, but not vertical, movements.

As in the measure of total distance in the animal activity monitor, the implanted animals evidenced a hyperactivity during the first 5 minutes they were in the open field. The hyperactivity, however, was gone once the animal had habituated to the field 55 minutes later. The effect was stronger in the implanted animals than lesioned only group, and reached significance only in the former case. Thus on two different measures of horizontal activity, including openfield and total distance, the implanted animals were relatively hyperactive.

The implants did not reverse the amphetamine induced hyperactivity. Indeed, the implanted group often appeared more hyperactive than the lesioned only group. The possible explanations for this, include (1) the implants did not functionally reconnect (or only partially did so) in the pathway that accounts for the amphetamine induced hyperactivity. Mason has postulated this pathway as involving connections between the striatum, substantia nigra, and nucleus accumbens, (2) physical characteristics of the implants were not correct, and did not mazimize the extent of possible recovery. Paramaters such as volume of the implanted tissue, age of donor tissue, time after injection, etc., all could have functioned as critical variables in the procedure, (3) the hyperactivity seen in the lesioned rats was not simply a function of striatal damage, but also resulted from distant lesions caused by the kainic acid, including lesions of CA3a-CA4 of the hippocampus, etc., (4) the pathology seen in the cortex facilitated the hyperactivity.

In summary, the findings on this behavior replicated and extended the amphetamine findings presented in experiment one. The females, like the males, were hyperactive following amphetamine injections, showing this hyperactivity only in the horizontal plane. The hyperactivity was not reversed by the implants. These findings further implicate the striatum in modulating locomotor activity, but restrict this modulation to the muscle groups involved in horizontal activity only.

(f) METRAZOL

There were no significant differences between groups on any of

the three metrazol measures. That quantitative differences were not obtained may be a function of the small number of animals, rather than a lack of an effect, as there was a trend for the lesioned animals to seize quicker and longer than controls. Thus the small number of subjects, and the large variance, make the negative results (with possible trends) difficult to interpret. Future experimentation will be required to more fully examine the role of the striatum in this behavior in female rats.

(vii) GENERAL DISCUSSION

The effects of kainic acid lesions in female Sprague-Dawley rats are similar to those seen in the male Wistar rats. First, the histopathological changes from the kainic acid lesions are similar. Both groups had large losses of intrinsic striatal neurons, enlargement of ventricles, and distant excitotoxic lesions in other regions of the neuraxis, including the hippocampus.

Second, both groups showed a number of behavioral deficits following the kainic acid lesions of the striatum that were similar. The females, like the males, showed profound deficits on T-maze performance, presumably because of deficits in either attention, concentration, encoding of memory, retrival of memory, or some combination therein. Like the males, the females also showed a profound hyperactivity in response to amphetamine injections. This experiment extended that finding by revealing that this hyperactivity occurred only in the horizontal, and not vertical, plane.

Third, a number of eating behaviors for female Sprague-Dawleys was similar to the findings for males. Both groups nonsignificantly

increased their ad lib food and water intake after kainic acid lesions, and significantly increased their 24 hour food intake following a day of starvation. Additionally, they showed a non-prandial hyperadipsia, drinking more water per gram of body weight than controls.

There were, however, three measures on which the female Sprague-Dawleys did not parallel the male Wistars. First, the females showed a subtle deficit in spontaneous locomotion in the animal activity monitor that did not exist in the males. This deficit may be a consequence of time after lesioning (i.e. the males were measured at 2 weeks, the females at 3 months). However, the lack of any significant changes in locomotor activity over the course of the experiment in the open field suggests that the females did not become progressively hyperactive over time, and thus argues against this explanation. As time after lesion is an unlikely explanation for the difference, the other uncontrolled for variables (i.e., sex/strain) must have accounted for the effect.

Secondly, the female kainic acid lesioned rats, unlike the males, gained weight after the kainic acid lesions. They did so while eating apparantly as much as the controls (the small number of rats makes this conclusion tentative), although they drank somewhat more. Furthermore, they lost less weight per gram of body weight during starvation than controls. It is unlikely that this effect in the female Sprague-Dawleys, but not male Wistars, is due to strain differences, as Wistar, Woodlyn, and CYF rats have been reported to show weight losses after kainic acid lesions. It is more likely that the sex differences accounted for the differential weight gain response. Thus it appears that the neural regulation of weight gain is dissimilar in the female rats and that, due to this effect, there is a lack of consistency in the

weight findings across sex.

Finally, the female rats did not show a significant change in the response to pentylenetetrazol, as did the males. This result is tentative, however, as the number of rats used on this measure were small, and as a trend in the lesioned group towards increased seizure response was found.

BEHAVIORAL EFFECTS OF THE IMPLANTS

The implants of fetal striatal tissue grew extremely well within the host striatum, and partially reversed both the cell loss and the behavioral deficits caused by the kainic acid lesions. The implanted group performed midway between controls and the lesioned only group on the T-maze. In addition, they showed less spontaneous hyperactivity than the lesioned only group in the activity monitors on three measures, including movement time, movement number, and rest time.

Conversely, the implants did not affect two of the lesion induced deficits. First, the hyperactivity in response to amphetamine injection was as intense in the implanted group as in the kainic acid lesions. Secondly, the deficit on the neurological exam appeared to be as impaired in the implanted animals as the lesioned only group.

Why the implants affected some behaviors, and not others, is unclear. It is possible that a number of paramaters of the implantation technique accounted for these continuing deficits. For example, it might have been that the donor fetal striatal cells needed to be carefully topographically implanted so as to return to their proper rostral/caudal and/or inferior/superior position in the recipient rat in order to maximally function in a behaviorally integrated manner. It was

possible that too many, or too few, cells were implanted. While the implanted animals had smaller ventricles than the lesioned only group anteriorally, as the implant thinned out more caudally the ventricular size increased and often became as large as that of the lesioned only group. Similarly, it was possible that contaminating tissue, such as tissue from the nucleus accumbens, was transplanted along with the striatal tissue and interfered with the ability of the implanted striatal tissue to behaviorally integrate. Finally, the time at which implantation was made could have represented a critical parameter, as the recipient brain may have had a maximal period of plasticity after the lesions were made, before or after which the extent of behavioral recovery was limited. Any one, or any combination of these or similar factors could have accounted for the remaining impairments in the implanted group.

It was also possible that the remaining deficits were due to distant effects of the kainic acid lesions in areas other than the striatum. For example, necrosis was seen in the neocortex whenever the implant was accidentally deposited there. Area CA3a-CA4 of the hippocampus was noted in two animals to have discrete lesions. This may have primarily caused, or been a secondary contributing factor, to the behavioral deficits which were not reversed, including deficits on the T-maze and the hyperactivity. It is highly possible that there were other, less obvious lesions not detected in the histology in a wide variety of other regions of the neuraxis which contributed to the neurological and hyperactivity deficits that remained. Thus distant lesions, not replaced by the implants, may have impacted on the extent of behavioral recovery.

Finally, the implanted animals evidenced several new behaviors

not seen in either the control or lesioned only groups. First, they showed a new type of spontaneous stereotypy behavior. They made many stereotypical movements, in a very short period of time, that habituated at a slower rate in the activity monitor, compared to the other two groups. Similarly, they were more active in their horizontal movements, both in the activity monitor and in the open field, than the other two groups. Thus the implants modified the spontaneous locomotor behaviors of the groups in subtle ways in the horizontal plane. These locomotor behaviors suggest that the implants functionally integrated within the host brain, and led to a change of behavior in the recipient animals.

The implanted animals also evidenced a different eating/weight gain pattern of behavior than the other two groups. Compared to controls, the implanted animals gained more weight over the course of the experiment, drank more water ad lib, and lost more weight during 24 hours of starvation. Compared to lesioned only, implanted animals showed an increase in weight gain at 6 weeks after implantation, drank nonsignificantly more, and ate significantly less after 24 hours of food deprivation. How the implants could exert this effect is unclear, but these results strongly suggest that the striatum in female rats regulates weight changes in a manner that is different from male rats.

(vii) SUMMARY AND CONCLUSIONS

In summary, this experiment found that the striatum of female rats influences a number of behaviors, including T-maze, spontaneous locomotion, weight gain, and amphetamine-induced locomotion. On two of these measures, including spontaneous locomotion and weight gain, the behavioral regulation of striatum appears different in the female rats

in comparison to the males. However, this result is tentative, and futher experimentation will be required to more systematically evaluate this issue.

Some of the deficits caused by the kainic acid lesion can partially be reversed by implants of fetal striatal tissue. In addition, the implants impacted on the recipient animal and modified their locomotor and feeding behavior. The reasons why the recovery was only partial is unclear. Futher experimentation will be needed to assess if the extent of recovery represents a minimal, maximal, or mid-point estimation of the ability of the implants to reverse lesion-induced deficits.

APPENDIX A

HUNTINGTON'S DISEASE

In 1872, George Huntington described a movement disorder characterized by 1) a tendency to insanity and suicide, 2) onset in adult life, and 3) a hereditary nature. The choreiform movements that accompany the disease are characterized by twisting movements of the trunk and distal extremities. The disease begins as an ordinary chorea might begin, by the irregular and spasmodic action of certain muscles, as of the face, arms, etc. The movements gradually increase, and muscles previously unaffected take on spasmodic action, until every voluntary muscle in the body becomes affected (Huntington, 1872). Huntington's Disease (HD), as it is now called, has since been found to be transmitted by an autosomal dominant gene with high penetrance (i.e., expression), and is found with a prevalance from 2-7 per 100,000 population (Kurtze & Kurland, 1973; Myrianthopoulos, 1973). It has been found in England (Bickford & Ellison, 1953; Brewis, Poskanzer, Rolland, & Miller, 1966; Heathfield, 1967), Iceland (Gudmundsson, 1969), Australia (Brothers, 1964), Poland (Kurtze & Kurland, 1973), America (Kurland, 1958; Kurtze & Kurland, 1973), Japan (Narabayashi, 1973), and Venezuela (Avilia-Giron, 1973) and has been described in those regions as having an annual incident rate of 0.5 per 100,000 population.

The essential pathology found in HD is a primary loss of nerve cells, especially the smaller ones, in the caudate nucleus and putamen (McMenemey, 1963). There is a significant loss of brain weight (Lange, Thorner, Hopf, & Schroder, 1976), accompanied by marked atrophy resulting in ventricular dilation. In addition, there is a poorly defined but generalized atrophy in the cerebral cortex and other parts

of the brain and spinal cord (Earle, 1973).

Pathological correlates in the caudate nucleus and putamen include a marked loss of neurons, a fine sponginess (i.e., a change in the texture of the brain), and moderate astrocytic gliosis (Bruyn, 1969; Earle, 1973; Klintworth, 1973). Although the small neurons tend to degenerate before the medium sized ones, both types of neurons are lost in advanced cases of the disease (Earle, 1973; McMenemey, 1963). The anterior quarter of the putamen and the head of the caudate, especially in inferior areas, are not often involved, as it is particularly the middle and posterior regions of the putamen where the atrophy is found, and the extent of the disease here is greater than in the caudate nucleus (Dom, Baro, & Bruchor, 1973; McMenemey, 1963).

Although cell changes do not usually occur in either the globus pallidus or the subthalamic nucleus, occasionally they are severely involved, as is the centromedian and dorsal medial nucleus of the thalamus (Forno & Jose, 1973; McMenemey, 1963). The degeneration which occurs in the cerebral cortex is primarily due to a reduction in neurons of layers 3, 5, and 6, often with the frontal and prefrontal cortex particularly affected (Forno & Jose, 1973; Klintworth, 1973; McMenemey, 1963). The cause of these degenerative changes is unknown.

A number of variants from the classical form of HD (i.e. progressive, uncomplicated chorea accompanied by dementia) have been described (Stevens, 1973). Most frequently, a juvenile and rigid variant (also called the Westphal variant) are recognized. The juvenile variant refers to those patients with an onset of symptoms, including chorea and mental deterioration, when they are less than 20 years old (Stevens, 1973). The prevalance of the juvenile type involves approximately 5% of all cases of HD, with an equal preponderance among

males and females (Bruyn, 1973; Korenyi & Whittier, 1967). Among affected parents of juvenile cases, fathers are more often the diseased parent than mothers (Bruyn, 1973). Clinical features include a severe dementia (decreased intelligence), dysarthria (abnormal speech), facial apraxia (loss of skilled movements of the facial muscles), dystonic posturing (abnormal muscle tone), and a tendency to mutism and depression with frequent suicidal ideation (Bruyn, 1973).

The Westphal variant of HD, also called the rigid-hypokinetic form, contains those patients with rigidity which may present as the dominant feature, or may appear only toward the end of the clinical course of the disease and never predominate (Stevens, 1973). The overall mean age at onset of rigidity is lower than for classical patients (Bittenbender & Quadfasel, 1962; Stevens, 1973), while the incidence of the disease is equal in males and females, both for rigid patients and their affected parents (Stevens, 1973). It is frequently accompanied by a bradykinesia, and the patients with the Westphal variant often live longer after diagnosis than do patients suffering from the classical disorder (Liss, Paulson, & Sommer, 1973). Histopathologically, the red nucleus and substantia nigra are somewhat more likely to be affected than the pallidum in comparison to the classical type. Other pathological changes include a demyelinating process in the periventricular area and the caudate, as well as the other traditional features of classical HD (Liss, Paulson, & Sommer, 1973).

The etiology of HD is unclear, and there is no treatment for the underlying disorder, although management of the symptoms that occur in the disease has improved. Phenothiazines and butyrophenones are effective in decreasing the frequency of choreiform movements (Bruyn,

1973; Korenyi & Whittier, 1967; Whittier, 1968). Twenty-two percent of all patients with HD are treated with anticholinergic agents, although some authors claim that these medications have never been shown to be beneficial and have been shown to worsen chorea (Klawans & Ruboirts, 1972; Ringel, Guthrie, & Klawans, 1973). Most patients tried on L-DOPA therapy have worsened on this medication, with the exception of patients with the rigid-akinetic form of the disorder, who improve with it (Ringel, Guthrie, & Klawans, 1973). Antidepressants are often prescribed when the emotional disturbances of the disorder include depression and/or suicidal ideation (Whittier, 1973). Aside from these symptomatic treatments, the prognosis for HD is as poor as when it was first described by Huntington in 1872---it is always terminal.

As of 1973, the experimental models of HD included 1) the induction of choreiform movements (i.e. twisting movements of the trunk and distal extremities) similar to HD in Parkinsonian patients treated with large doses of L-DOPA, and 2) the induction of chorea by L-DOPA in patients who inherited the autosomal dominant gene of HD but who did not previously develop chorea (Earle, 1973). Beginning in the 1970's, the first studies using kainic acid to make neostriatal lesions in the rat were done. These results suggested that pathologically and biochemically, rats with kainic acid lesions developed neuropathological changes that resembled the human neuropathology seen in HD (Coyle, Schwarcz, Bennett, & Campochiaro, 1977; Coyle, 1983; McGeer & McMeer, 1976; Schwarcz & Coyle, 1977a; 1977b). Since that time, a great deal of work has been done examining the effects of kainic acid lesions in the rat striatum, partially in an effort to determine the suitability of kainic acid as an experimental model for HD.

BEHAVIORAL SIMILARITIES BETWEEN HD AND RATS WITH KAINIC ACID LESIONS

The behavioral deficits occurring after kainic acid lesions of the striatum in rats, like the pathological and biochemical changes, have been reported to be similar to those of HD. Humans with HD exhibit episodes of violent outbursts and periods of depression (Boll, Heaton, & Reitan, 1974; Garron, 1973). Sanberg, Pisa, and Fibiger (1978) have found that rats with kainic acid lesions of the striatum show significantly more thigmotaxic (i.e., wall hugging) behavior, explore less than controls when placed in a novel setting, and have significantly longer latencies both to leave the start box and to eat the first food pellet in the goal box in a T-maze. They characterized such behavior as representing a fearful response on the part of the animal (Sanberg, Pisa, & Fibiger, 1978). Based on this and previous work, Sanberg, Pisa, and Fibiger (1978) concluded that these behaviors represented increased fearful responses in the kainic acid lesioned animals, and that this is the animal counterpart to the emotional lability seen in humans.

Frequently there is a progressive intellectual deterioration in the form of a global and severe dementia in humans with HD, with a resulting impairment of learning, memory, and judgment (Garron, 1973; Sistha, Troupe, Marszalek, & Kremer, 1974). Impairments in T-maze performance, passive and active avoidance, and other simple learning paradigms are seen in rats with kainic acid lesions of the striatum (Divac et al., 1978; Pisa, Sanberg, & Fibiger, 1978; Sanberg, Lehmann, & Fibiger, 1978). Fibiger (1978), Sanberg (Sanberg, Pisa, &

Fibiger,1979a; 1979b; Sanberg, Pisa, & Fibiger, 1978) and Divac et al. (1978) have likened these deficits to those seen in HD, and argue that the impairments on these simple tasks are the animal equivalent to the human dementia that accompanies HD.

(F) KAINIC ACID LESIONS OF THE STRIATUM AS THE MODEL OF THE WESTPHAL VARIANT OF HD

Perhaps the most dramatic characteristic of HD is the twisting, distorting movements that accompany the condition. For the kainic acid rat model of HD to be considered a good behavioral model of the human condition, the lesioned rats should show some parallel to these twisting human movements. Mason (1981) argued that the lesioned rats do demonstrate choreiform movements. He stated that, because rats do not have fine control of forepaw movements, they can only manifest chorea in the form of a locomotor abnormality. Specifically, he claimed that the increased nocturnal locomotion, hyperreactivity to sound and touch, and occasional violent loss of control of motor inhibition of rats with kainic acid lesions of the striatum should be considered a rodent version of chorea. Pisa (1982), in a rebuttal to Mason, concluded that the abnormal movements present in the human condition simply do not exist in the rat model. He argued that increased locomotor activity and decreased forearm praxis do not equate to choreiform movements. Although choreiform movements are seen in rats lesioned with other methods (Pisa, 1982), they do not occur in the model.

This lack of grossly abnormal movements in the rat model of HD argues against its similarity to the classical form of the illness. However, kainic acid lesions of the striatum in the rat roughly

parallels the Westphal variant of HD. Both lack choreiform movements. Both have similar pathological and biochemical changes in the brain, with prominent striatal cell loss, decreases in choline acetyltransferase and glutamic acid decarboxylase, increases or no change in dopamine and tyrosine hydroxylase, and a wide variety of accompanying lesions in other areas of the neuraxis. Both lead to epileptic activity, with increased grand mal and focal seizures, as well as decreased seizure threshold to seizure inducing stimuli. Both are accompanied by deficits in learning and memory, with the rats unable to perform on simple T-maze and avoidance tasks, while the humans show dramatic decreases in IQ as they dement over the course of the illness. Finally, the rats show dramatic increases in activity after administration of amphetamine. Similarly, amphetamine also causes an increase in the choreiform movements in the normal variant of HD (Klawans & Weiner, 1974). (Note: I am aware of no published literature on the effect of amphetamine in humans with the Westphal variant of HD.)

Thus, morphologically, pathologically, biochemically, and on simple tests of learning, the kainic acid model of HD roughly parallels that of the Westphal (rigid-hypokinetic) form of the condition. This circumstantial evidence has led a number of authors (see Coyle, 1983, for review) to suggest a possible etiological role of glutamate in the onset of HD (kainic acid is thought to exert its neurotoxic effect by exciting glutamate receptors). However, there is no substantive link to date that supports the role of glutamate in the cell loss of HD, and it remains as a tantalizing, but unproven, hypothesis.

APPENDIX B

BEHAVIORAL EFFECTS RESULTING FROM TRANSPLANTATION OF FETAL RAT BRAIN

This section will review the fetal brain transplant literature, which looms as a possible treatment intervention for the deficits caused by kainic acid lesions of the striatum.

The ability of the adult rat brain to serve as a growth medium for implanted embryonic neural tissue was first demonstrated in the early part of this century (Dunn, 1917; Ranson, 1914). Since then, cerebral cortex (Das, 1975; Das, Hallas, & Das 1980; Dunn, 1917; Labbe, Firl, Mufson, & Stein, 1983; Greene & Hildegarde, 1945; Legros Clark, 1940), locus coeruleus and raphe nuclei (Nygren, Olson, & Seiger, 1977; Stenevi, Bjorklund, & Sveendgaard, 1976), hypothalamus (Arendash & Gorski, 1982; Gash, Sladek, & Sladek, 1980; Gash & Sladek, 1980; Krieger, Perlow, Gibson, Davies, Zimmerman, Ferin, & Charlton, 1982; Stenevi, Bjorklund, Kromer, Paden, Gerbach, & McEven, 1980), tectum (Lund & Hauschka, 1976; Mcloon & Lund, 1983), Schwann cells (Blakemore, 1977; Rosenstein & Brightman, 1979), septal nuclei (Bjorklund, Kromer, & Stenevi, 1979; Bjorklund & Stenevi, 1977), dentate granule cells (Sunde & Zimmer, 1981), hippocampus (Kromer, Bjorklund, & Stenevi, 1980; Segal & Landis, 1974), substantia nigra (Bjorklund & Stenevi, 1979; Bjorklund, Schmidt, & Stenevi, 1980; Dunnett, Fray, Bjorklund, Stenevi, & Iversen, 1981; Dunnet, Bjorklund, Stenevi, & Iversen, 1981; Freed, Perlow, Karoun, Seiger, Olson, Hoffer, & Wyatt, 1980; Perlow, Freed, Hoffer, Seiger, Olson, & Wyatt, 1979; Perlow, 1980; Stenevi, Bjorklund, & Dunnett, 1980; Gage, Dunnett, Stenevi, & Bjorklund, 1983), autonomic ganglia (Ranson, 1914; Rosenstein & Brightman, 1979; Zimmer, Lawrence, & Raisman, 1980), striatum (Deckel, Robinson, & Sanberg, 1983; Kimura,

McGeer, & McGeer, 1980; Schmidt, Bjorklund, & Stenevi, 1981), and cerebellum (Das, 1973; 1975; 1977; Das & Altman, 1971; 1972; Das, 1977; Das & Hallas, 1978; Das, Hallas, & Das, 1979; 1980) all have been shown to grow and acquire adult morphological characteristics when grafted from fetal rats into the brains of adult rats.

The implanted fetal tissue increases its initial implanted size (Bjorklund, Dunnett, Stenevi, Lewis, & Iversen, 1980; Kromer et al., 1981; Olson, Freedman, Seiger, & Hoffer, 1977) and shows from 60-95% survival rates, depending on the method of implantation used (Bjorklund & Stenevi, 1977; Das et al., 1979). The basic characteristics of the successful implantation, as defined by the growth, survival, cellular and cytoarchitectural differentiation of the implants, their anatomical continuity with the host brain, and survival for life of the host animals (i.e., the animals that receive the implants), are not significantly altered by the age of the donor embryos, the age of the host animals, or the site of the host brain where the grafts are implanted (Hallas, Das, & Das, 1980). However, other morphological characteristics of the implants, such as the magnitude of their growth and the nature of cellular and cytoarchitectural differentiation, all seem to be influenced greatly by the age of the donor embryos and the type of neural tissues used as the grafts (Das et al., 1980). The neural tissue may have large or small growth potential, but its final growth is determined, to some extent, by the physical room available in the host brain and the degree of pliability, or resistance, offered by the host brain tissue and the cranium (Das et al., 1980).

Far from being inert in its interaction with the host brain, the implanted neural tissue interacts extensively with the recipient CNS. Somatic differentiation, synaptogenesis, gliogenesis, and myelogenesis

all proceed in the implant at a rate that closely mimics that of its *in vivo* homologue (Das, 1975; Das & Altman, 1972; Mollgard, Lundberg, Beebe, Bjorklund, & Stenevi, 1978; Rosenstein & Brightman, 1978; Stenevi, Bjorklund, et al., 1980). Myelination of the recipient's neural tissue (Blakemore, 1977; Rosenstein & Brightman, 1979; Thuline & Bunge, 1972), and induction of mitosis in host neurons located close to the implants (Bjorklund et al., 1979; Das, 1975; Jaeger & Lund, 1979; Kromer et al., 1980; 1981; Perlow, 1980; Thuline & Bunge, 1972) have all been reported. Many of the anatomical connections have been found to be physiologically patent. For example, intracerebral implanted fetal eyes (day 15 gestation) yield electrical electroretinograms in the host in response to flashes of light (Lund, 1976); implantation of fetal vasopressin secreting hypothalamic tissue secretes quantities of vasopressin capable of reversing diabetes insipidus (Gash & Sladek, 1980; Gash, Sladek, & Sladek, 1980); fetal hippocampal grafts to the vitreous fluid of the eye show spontaneous electrical activity that is responsive to pharmacological activation (Hoffer, Seiger, Ljundberg, & Olson, 1974; Olson, Freedman, Seiger, & Hoffer, 1977).

Implantation of fetal caudate-putamen tissue into adult host rat brains with previous kals of the striatum have been found to grow robustly (Deckel, Robinson, Coyle, & Sanberg, 1983; Deckel, Robinson, & Sanberg, 1983; Kimura et al., 1980; Schmidt et al., 1981), and histologically have the appearance of large solid tissue composed of medium sized neuronal perikarya, easily distinguished from the neuron poor surrounding gliotic areas of the host striatum (Schmidt et al., 1981). There is an *in situ* proliferation of implanted neuroblasts that mature fully over time. At 7 weeks posttransplant survival, these implanted cells lead to a large recovery of the CAT and GAD containing

neurons that are normally seen in the caudate-putamen; only levels of dopamine in the implanted striatum do not fully recover (Schmidt et al., 1981).

Transplants in a number of different areas in the rat brain have been found to influence the behavior of the host animal. Such work has been done in the substantia nigra and caudate nucleus (Bjorklund, Dunnett, Stenevi, Lewis, & Iversen, 1980; Bjorklund, Schmidt, & Stenevi, 1980; Bjorklund & Stenevi, 1979; Dunnett, Bjorklund, Stenevi, & Iversen 1981; Dunnett, Schmidt, Bjorklund, Stenevi, & Iversen, 1981; Fray et al., 1983; Freed et al., 1980; Perlow et al., 1979; Perlow, 1980; Gage et al., 1983), the striatum (Deckel, Robinson, Coyle, & Sanberg, 1983; Deckel, Robinson, & Sanberg, 1983), the septum (Bjorklund, Kromer, & Stenevi, 1979; Dunnett et al., 1982; Dunnett, Schmidt, Bjorklund, Stenevi, & Iversen, 1982), the hypothalamus (Arendash & Gorski, 1982; Gash & Sladek, 1980; Gash et al., 1980; Krieger et al., 1982), the cerebellum (Wallace & Das, 1982), and the frontal cortex (Labbe et al., 1983). Much of the behavioral work done has used rats first lesioned with 6-hydroxydopamine (6-OHDA) in the area of the nigro-striatal tract. This paradigm was chosen because 1) it is a highly specific lesion for the dopaminergic fibers that enter the striatum from the substantia nigra, 2) it allowed researchers easy access to the deafferented striatum for depositing implanted tissue, and 3) previous experimental work demonstrated that implants of embryonic substantia nigra into cavities superior to the striatum robustly reinnervated the host striatum in a pattern similar to that of the endogenous substantia nigra (Bjorklund, Dunnett, Stenevi, Lewis, & Iversen, 1980; Bjorklund, Schmidt, & Stenevi, 1980; Bjorklund & Stenevi, 1979; Perlow et al., 1979). In the earliest study done with this model, Perlow and coworkers

(Perlow et al., 1979; Freed et al., 1980; Perlow, 1980) implanted fetal rat dopaminergic neurons adjacent to the caudate nucleus of adult recipients whose endogenous dopamine input had been destroyed 2-4 months previously with 6-OHDA. The grafts, placed in the lateral ventricle, not only survived and proliferated, but reversed apomorphine induced rotation (i.e., rotation seen in animals with ipsilateral 6-OHDA lesions when they are administered i.p. apomorphine). Bjorklund and coworkers (Bjorklund, Dunnett, Stenevi, Lewis, & Iversen, 1980; Bjorklund, Schmidt, & Stenevi, 1980), using a higher dose of apomorphine, failed to replicate the reduction of apomorphine induced turning. This discrepancy was resolved by Dunnett, Schmidt, Bjorklund, Stenevi, and Iversen (1981). These authors were able to replicate Bjorklund et al.'s study, finding that both grafted, and lesioned only, rats expressed equal contralateral rotation at a dose of 0.25 mg/kg of apomorphine. However, implanted animals showed a marked reduction in rotation compared to lesioned only animals at the lower dose of apomorphine, thus replicating Perlow and Freed's work (Perlow et al., 1979; Freed et al., 1980). They interpreted these findings as suggesting that there was a partial reduction in apomorphine supersensitivity following dopaminergic reinnervation of the striatum, producing a shift in the apomorphine dose-response curve to the right. They also found that the reduction in the dopamine receptor sensitivity in the lesioned striatum correlated with the extent of the reinnervation from the implant. Like Perlow et al. (1979), they concluded that the implants reinnervate the lesioned area and function on a behavioral level as part of the host brain.

Implants of substantia nigra in animals with previous striatal 6-OHDA lesions decreased the relative hyperactivity seen in these animals in response to amphetamine. Implanted, but not lesioned only,

rats showed a decrease in ipsilateral rotation induced by 5 mg/kg amphetamine (Bjorklund, Schmidt, & Stenevi, 1980; Dunnett, Schmidt, Bjorklund, Stenevi, & Iversen, 1981). At 3 months after implantation, there is a compensation of the amphetamine induced rotation directly correlated with the density and extent of the dopamine reinnervation from the implant into the dorsal caudate-putamen (Bjorklund, Dunnett, Stenevi, Lewis, & Iversen, 1980). As with the apomorphine results, this has been interpreted as evidence that the implants are functionally integrating within the host brains. Thus, substantia nigra implants to 6-OHDA lesioned striatum ameliorate rotation induced by either a presynaptic (amphetamine) or a postsynaptic (apomorphine) dopamine agent.

In addition to these effects, substantia nigra implants in animals with previous 6-OHDA lesions of the striatum change locomotor activity. The implanted rats show less asymmetry in spontaneous behavior than lesioned controls (Dunnett, Schmidt, Bjorklund, Stenevi, & Iversen, 1981). In addition, following a second 6-OHDA lesion, implanted rats show a significant increase in spontaneous activity compared to controls (Dunnett, Schmidt, Bjorklund, Stenevi, & Iversen, 1981). In addition, they show a sensorimotor bias away from the side of the implant. These effects on locomotor behavior indicate that the implants do not simply affect receptor sensitivity to dopamine agonists, but rather fundamentally integrate within the host brain to modulate spontaneous as well as pharmacologically manipulated locomotor behavior.

In addition to their ability to decrease spontaneous and drug induced motor abnormalities, fetal substantia nigra implants are capable of sustaining intracranial self-stimulation (ICSS) in adult rats with previous striatal 6-OHDA lesions. Fray et al. (1983) found that several

months after implantation, substantia nigra grafted rats reinnervated 1/8 to 1/3 of the total volume of the head of the dorsal striatum. After this reinnervation was complete, the grafted rats bar pressed to produce a reinforcing electric current more frequently than sham implanted controls. This effect occurred at 4 months after implantation. Rats in which the nigral graft failed to provide dopamine reinnervation of the dorsal striatum, and rats receiving grafts not containing dopaminergic neurons, all failed to exhibit ICSS. This finding indicates that the reinnervation of the dorsal striatum by the implant has more than just an anatomical effect, because the animal behaved differently under the experimental conditions. The authors concluded that the grafts sustained ICSS, and physiologically, behaviorally, and histochemically integrated with the host brain.

In a similar paradigm, substantia nigra grafts to rats with unilateral 6-OHDA lesions of the striatum have been shown to influence spontaneous choice behavior on a T-maze (Dunnett, Schmidt, Bjorklund, Stenevi, & Iversen, 1981). Non-implanted rats with these lesions perseverate on a T-maze, choosing the arm of the maze ipsilateral to the side of the lesion 97% of the time. Implanted rats perseverated only 60-70% of the time, alternating on 30-40% of the trials. Again, this was interpreted as evidence that the grafts are having a behavioral effect on spontaneously behaving host animals.

Finally, Gage et al. (1983) recently reported that rats of 21 to 23 months of age successfully sustained fetal nigral dissociated cell suspension implants. Twelve weeks after implantation, the aged rats with nigral grafts, but not the aged controls or septally grafted rats, had significantly improved their balance and limb coordination. The grafts had no effect on hypoactivity in the aged rats, nor on their

ability to vertically descend a wire mesh. They concluded that the nigral grafts had reversed some of the age related motor abnormalities in the animals, and might offer one particular route of treatment for dementing processes.

Thus on a number of different measures, including apomorphine and amphetamine induced rotation, spontaneous rotational behavior, T-maze side preference, and ICSS, implanted fetal substantia nigra tissue behaviorally integrates with the host brain and changes the behavior emitted by the grafted animal.

The substantia nigra is not the only region of the rat brain which has been found to be capable of altering host animal behavior when grafted into the animal. Septal implants have been able to alleviate behavioral deficits following fimbria/fornix lesions (Dunnett et al., 1982). These lesions interfere with the ability of the rat to learn a rewarded alternation task in a T-maze, presumably because they remove all cholinergic innervation of the hippocampus by interrupting septal-hippocampal projections. Following implantation of fetal septum into the lesioned area, the hippocampus is reinnervated with cholinergic fibers in a way that closely resembles the in vivo pattern (Bjorklund, Kromer, & Stenevi, 1979; Bjorklund & Stenevi, 1977; Dunnett et al., 1982; Lewis, Mueller, & Cotman, 1980). Following cholinergic reinnervation, partial recovery on the T-maze was found (Dunnett et al., 1982), and the rats were able to relearn the paradigm, although at a rate slower than the controls. The authors explained this finding by postulating that the fimbria/fornix lesions decreased both spontaneous and rewarded alternation of the animal. While the decreased rewarded alternation was reinstated by the implants, they felt that the decreased spontaneous alternation was not. It was this decrease in spontaneous

alternation which accounted for the early decreased performance in the rewarded alternation paradigm. Dunnett et al. (1982) attributed the recovery of the rewarded alternation to the septal implants. Further evidence supporting this conclusion came from the finding that the degree of recovery in the rewarded alternation task was correlated with acetylcholinesterase positive fiber ingrowth into the hippocampus from the implants.

A fundamentally different demonstration of the ability of implanted fetal brain to integrate with recipient brain has come from assessing endocrinological changes accompanying hypothalamic implantation. In the earliest of these studies, Gash and coworkers (1980) were able to partially reverse diabetes insipidus in Brattleboro rats (rats with a genetic deficiency of vasopressin) by implanting normal fetal hypothalamic tissue into the lateral ventricle of the adult Brattleboro. While not all rats recovered, implanted rats significantly decreased their fluid intake and output in comparison to controls. Their findings suggested that the implanted tissue was capable of regulating osmotic homeostasis in the recipient rats, presumably by interacting appropriately with the host neuroendocrine system.

In an attempt to assess whether transplanted animals changed in their behavior, Arendash and Gorski (1982) implanted neonatal male preoptic tissue into ovarectomized female neonatal rats, and assessed masculine and feminine sexual behavior in the recipients during adulthood. The implanted females showed substantially more male sexual behavior, as measured by mounts and intromissive responses, in any single test than did females receiving caudate nucleus, sham, or unilateral medial preoptic area implants. Female sexual behavior, as measured by lordotic responses, were increased in animals that received

preoptic or amygdala tissue, but not caudate or sham lesioned animals. The authors concluded that the implants developed functional connections as evidenced by significantly higher levels of male and female behavior displayed by the female recipients as adults.

In a conceptually similar experiment, Krieger et al. (1982) implanted fetal hypothalamic tissue into adult male hpg mice (mice with a deficiency of GnRH---hypothalamic gonadotropin releasing hormone). The hpg mouse has immature reproductive organs, small abdominal testes, and low pituitary and plasma gonadotropin levels. Two months after implantation of fetal preoptic area from day 17-18 fetal mice into the anterior third ventricle of the hpg mouse, preoptic area grafts contained GnRH neurones with GnRH positive fibres entering capillaries of the median emminence. Hypothalamic GnRH, and pituitary and plasma gonadotropin concentrations, were increased compared to hpg only. In addition, testes of the mice were enlarged and had descended into the scrotum from the abdomen. There was evidence of full spermatogenesis, and there was development of interstitial testicular cells. No such effects were seen with control cortical tissue implants. The conclusion drawn from these findings was that the implanted hypothalamic tissue not only integrated with the host brain, but did so in such a way that it reversed the expression of the genetic deficit.

Wallace and Das (1982) reported that implanting fetal cortical tissue into rat cerebellum also leads to functional integration of the implant with the recipient host brain. However, their results are difficult to interpret. The authors used three groups, a lesioned only, an implanted only, and a control lesioned group. They performed an aspiration lesion on the lesioned group, but did not similarly lesion the transplanted group. Instead, they claimed that the implanted

cortical tissue produced a pressure lesion in the cerebellum because of its growth, causing an equivalent amount of neuronal damage as did the aspiration lesion. Behaviorally, they found that the transplanted group resembled the control group on an elevated walkway test, a neurological exam, and on open field. They interpreted these findings as suggesting that the fetal cortical tissue, in making synaptic connections with the host cerebellum, somehow ameliorated the behavioral deficits. Unfortunately, an alternative explanation is that the difference between groups was not accounted for by the positive effects of the implants, but by lack of a pressure lesion. As only one group, the lesioned group, was given these lesions, only this group showed the effects.

Recently, Labbe et al. (1983) assessed the ability of frontal and cerebellar fetal tissue to reverse deficits in spatial (i.e., T-maze) alternation in rats with bilateral destruction of the medial frontal cortex. They found that implants of frontal cortex, but not cerebellum, facilitated recovery from the lesion. Animals with frontal cortical implants scored significantly better than the group given cerebellar tissue on days needed to make 9 of 10 choices correctly on a T-maze in one day, and on number of days needed to make 18 out of 20 choices correctly in 2 days. While implanted animals performed better than the lesioned only animals, control animals scored significantly better than all other groups on the spatial alternation task. The behavioral recovery occurred at only 14 days after implantation, and the authors postulated that the recovery of function might be due to factors other than connectivity between the implant and host brain, such as the production of polyamines or specific nerve factors, alteration of glial activity or neurotransmitter levels, or by changes in membrane receptor properties in the tissue surrounding the graft. Further investigation

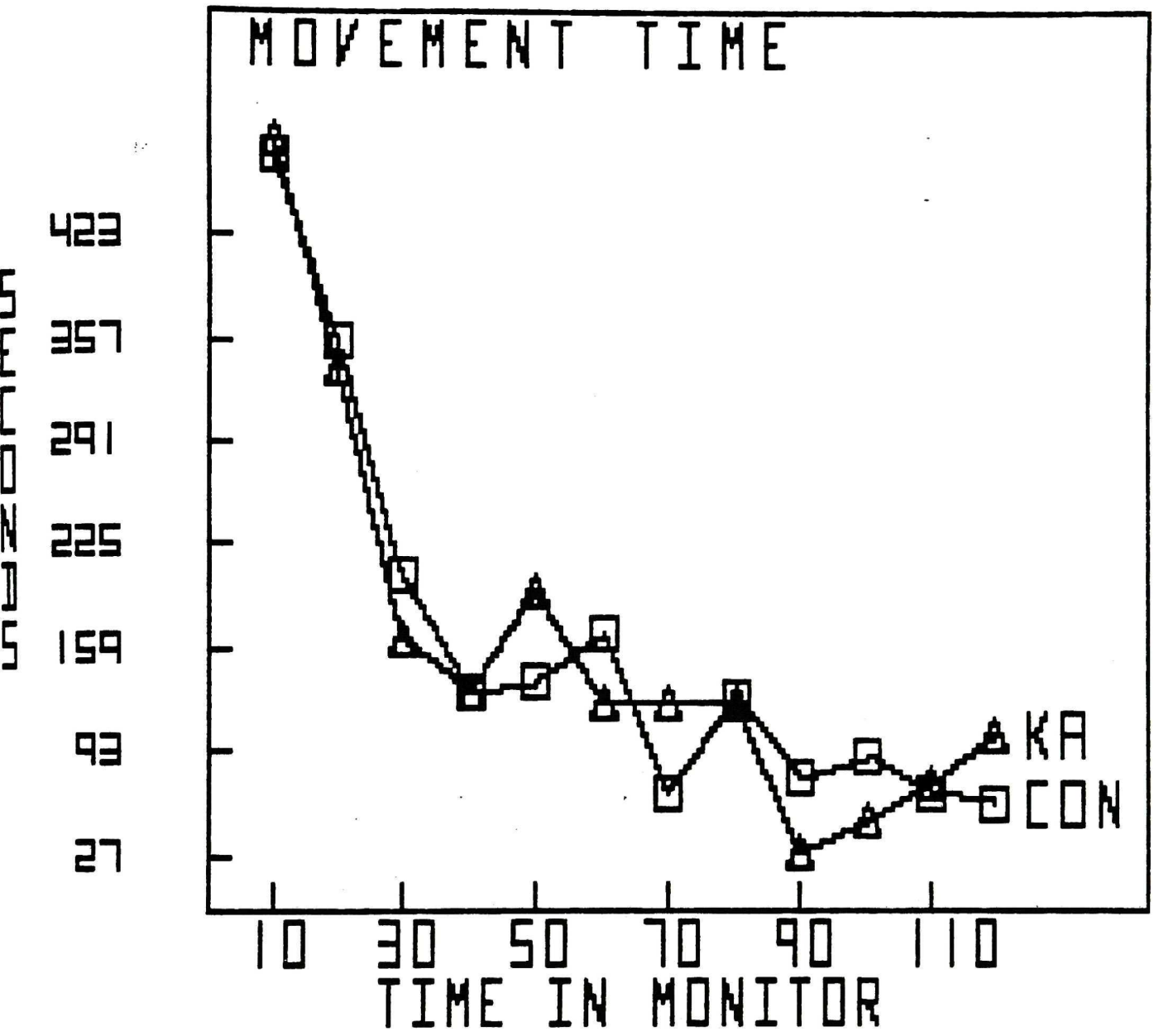
will be required to assess these possibilities. HRP injections done at least 78 days after implantation revealed projections to medial dorsal and anterior thalamic nuclei, as well as to the contralateral frontal cortex.

In summary, implants of fetal substantia nigra, frontal cortex, septum, and hypothalamus have been found to make anatomical and physiological connections within the recipient brain, and to change the behavior of the animals receiving the implants. To date, the behavioral effects of implantation of other regions of the fetal brain into other regions of the recipient animal's CNS has not been done.

APPENDIX C

MOVEMENT TIME ANOVA

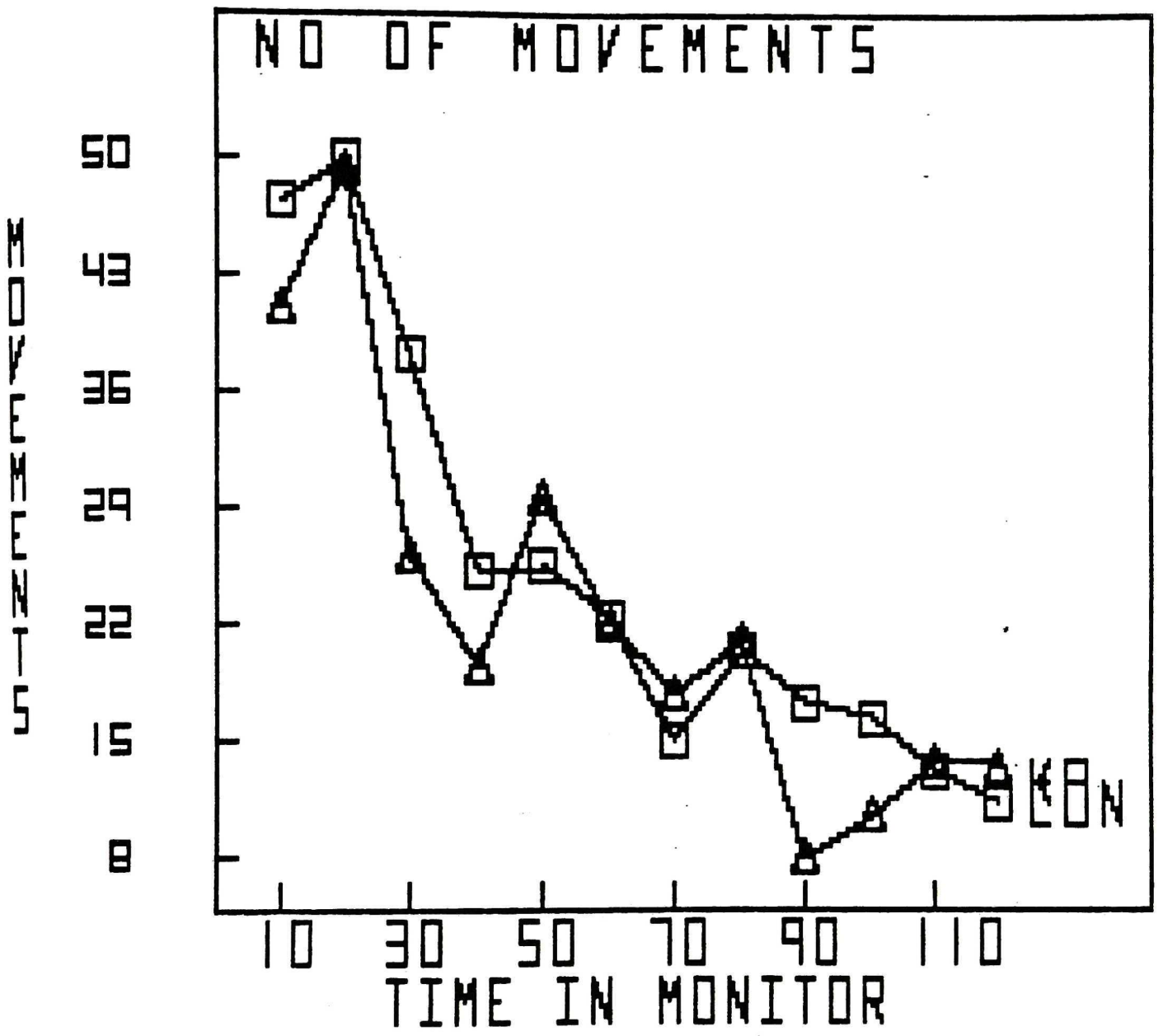
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	117.188	1	117.188	.003	
ERROR	432533.293	14	30895.235		
WITHIN SUBJECTS					
TIME IN MONITOR	2863477.360	11	260316.123	21.645	<.001
LESION X TIME	65720.940	11	5974.631	.497	
ERROR	1852085.710	154	12026.531		



This graph displays the mean number of seconds spent moving by the two groups of animals during the 120 minutes they were in the animal activity monitor. Squares are sham lesioned controls; triangles represent the kainic acid lesioned group.

NUMBER OF MOVEMENTS ANOVA

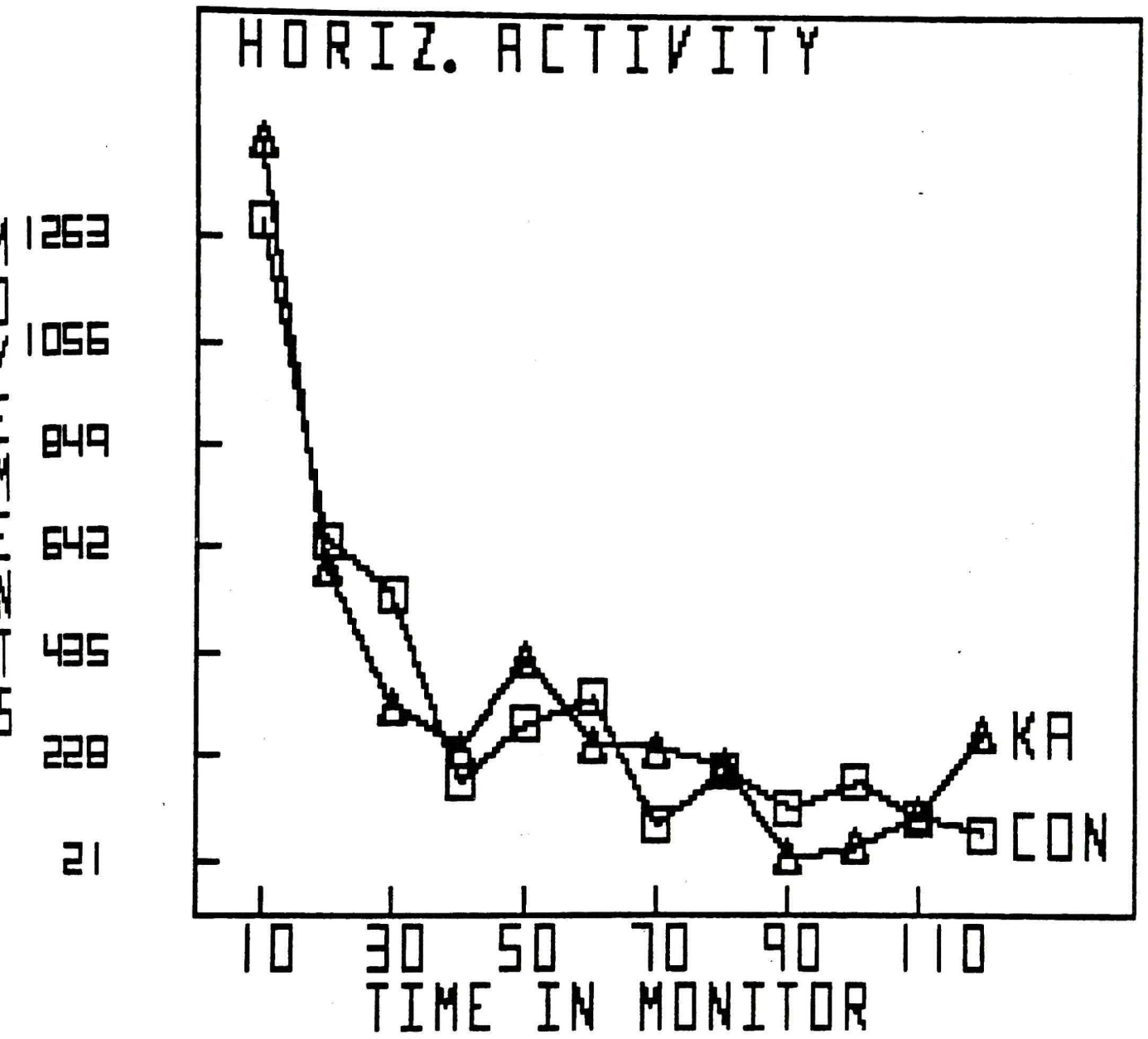
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	282.755	1	282.755	.264	
ERROR	14999.740	14	1071.410		
WITHIN SUBJECTS					
TIME IN MONITOR	27505.516	11	2500.501	12.329	<.001
LESION X TIME	1178.432	11	107.130	.528	
ERROR	31232.635	154	202.809		



This graph shows mean number of movements emitted by the male Wistar rats over the 120 minutes they spent in the activity monitor. Squares represent sham lesioned controls; triangles are kainic acid lesioned animals.

HORIZONTAL ACTIVITY ANOVA

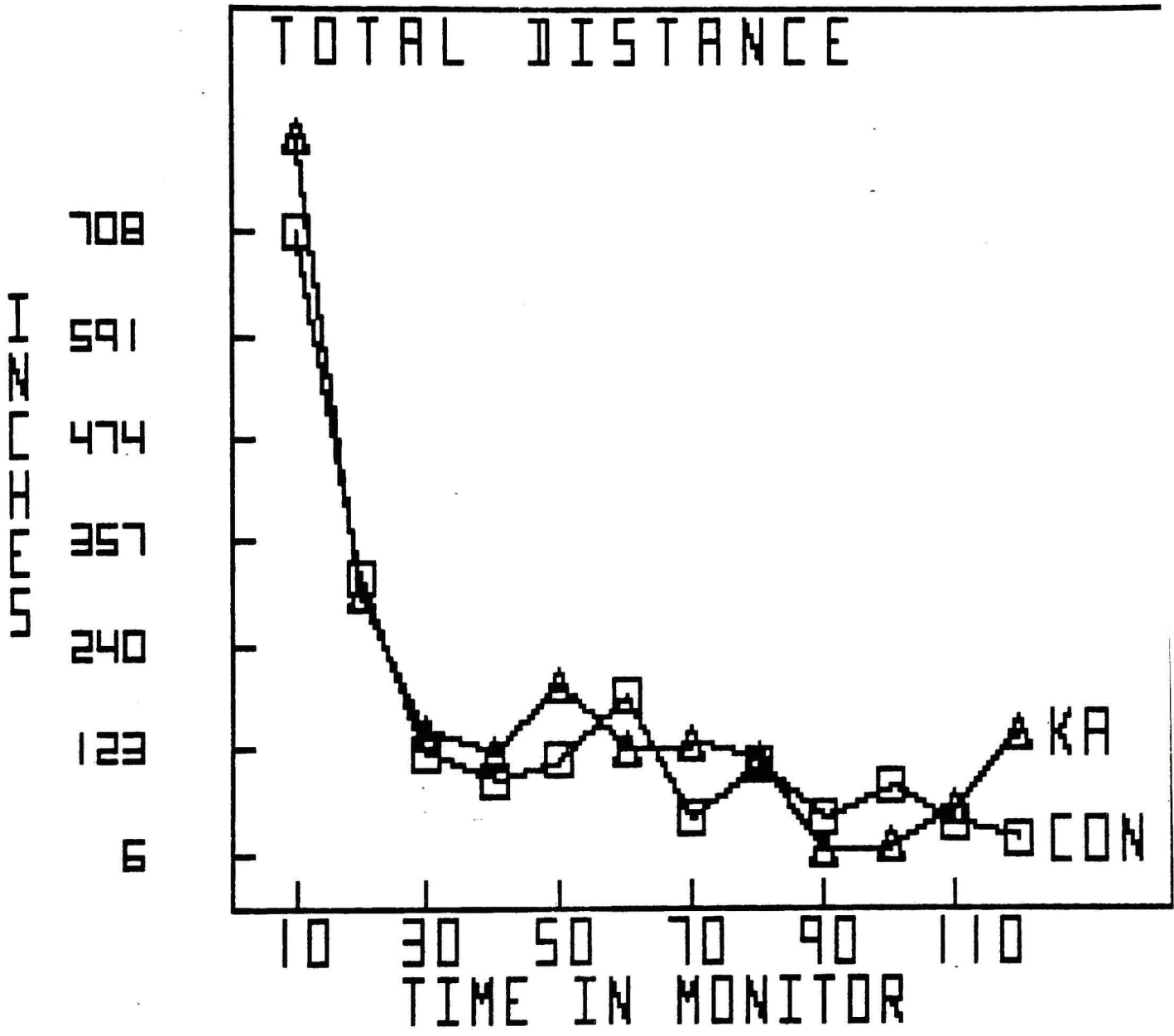
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	3771.875	1	3771.875	.024	
ERROR	2203959.0500	14	157425.646		
WITHIN SUBJECTS					
TIME IN MONITOR	23228190.80	11	2111653.710	17.754	<.001
LESION X TIME	816727.563	11	74247.960	.624	
ERROR	1831684.400	154	118940.678		



Mean number of horizontal movements emitted by the two groups of male Wistar rats is displayed over the 120 minutes they were in the activity monitor. Squares represent sham lesioned controls; triangles represent kainic acid lesioned controls.

TOTAL DISTANCE ANOVA

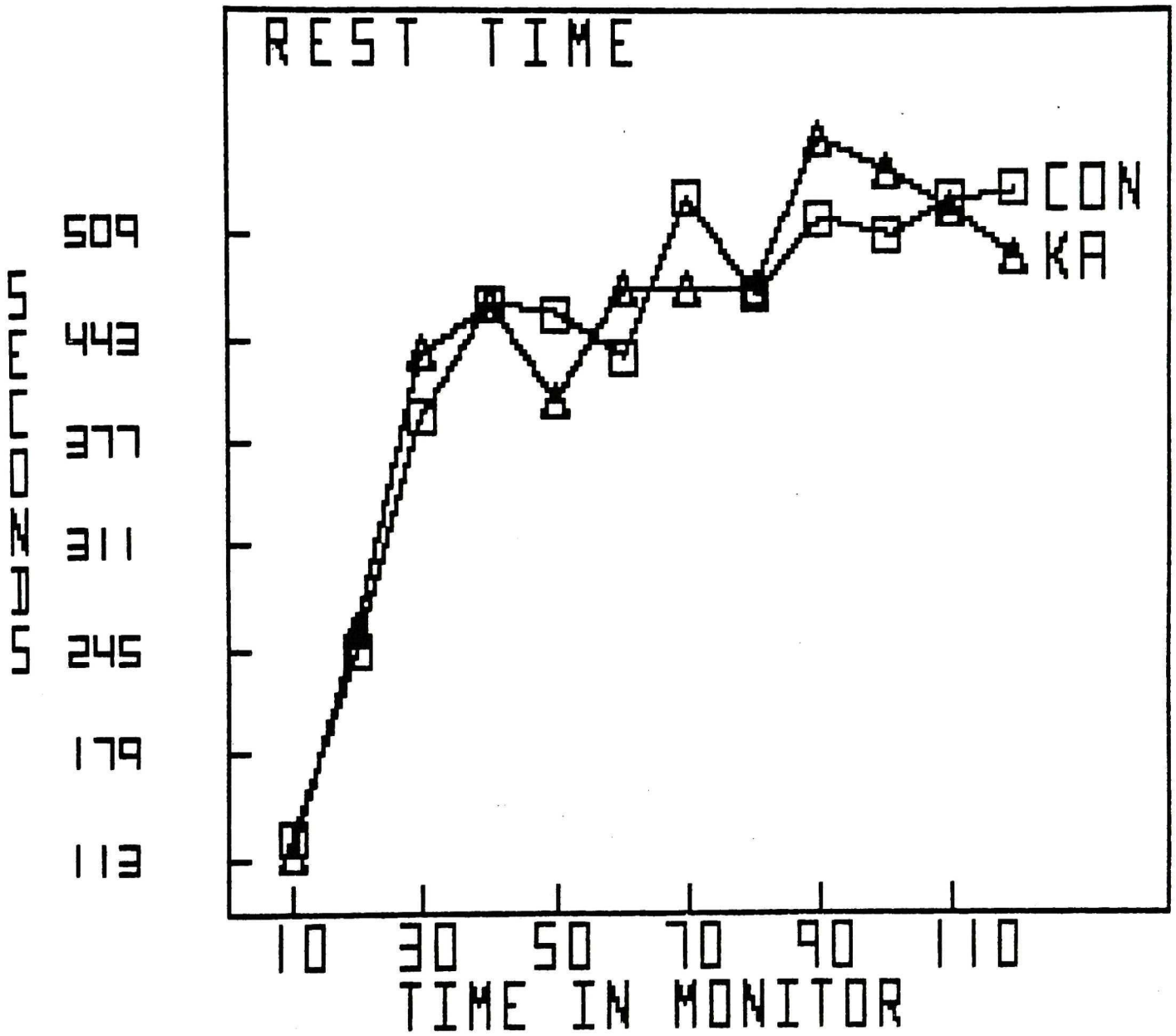
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS	29700.750				
LESION	29700.750	1	29700.750	.834	
ERROR	498583.752	14	35613.125		
WITHIN SUBJECTS					
TIME IN MONITOR	7181755.290	11	652886.845	24.683	< .001
LESION X TIME	185476.879	11	16861.534	.637	
ERROR	4073510.000	154	26451.364		



This figures shows mean number of inches travelled by each of the 2 groups of animals during their 120 minutes in the activity monitor. Squares represent sham lesioned controls; triangles are kainic acid lesioned rats.

REST TIME ANOVA

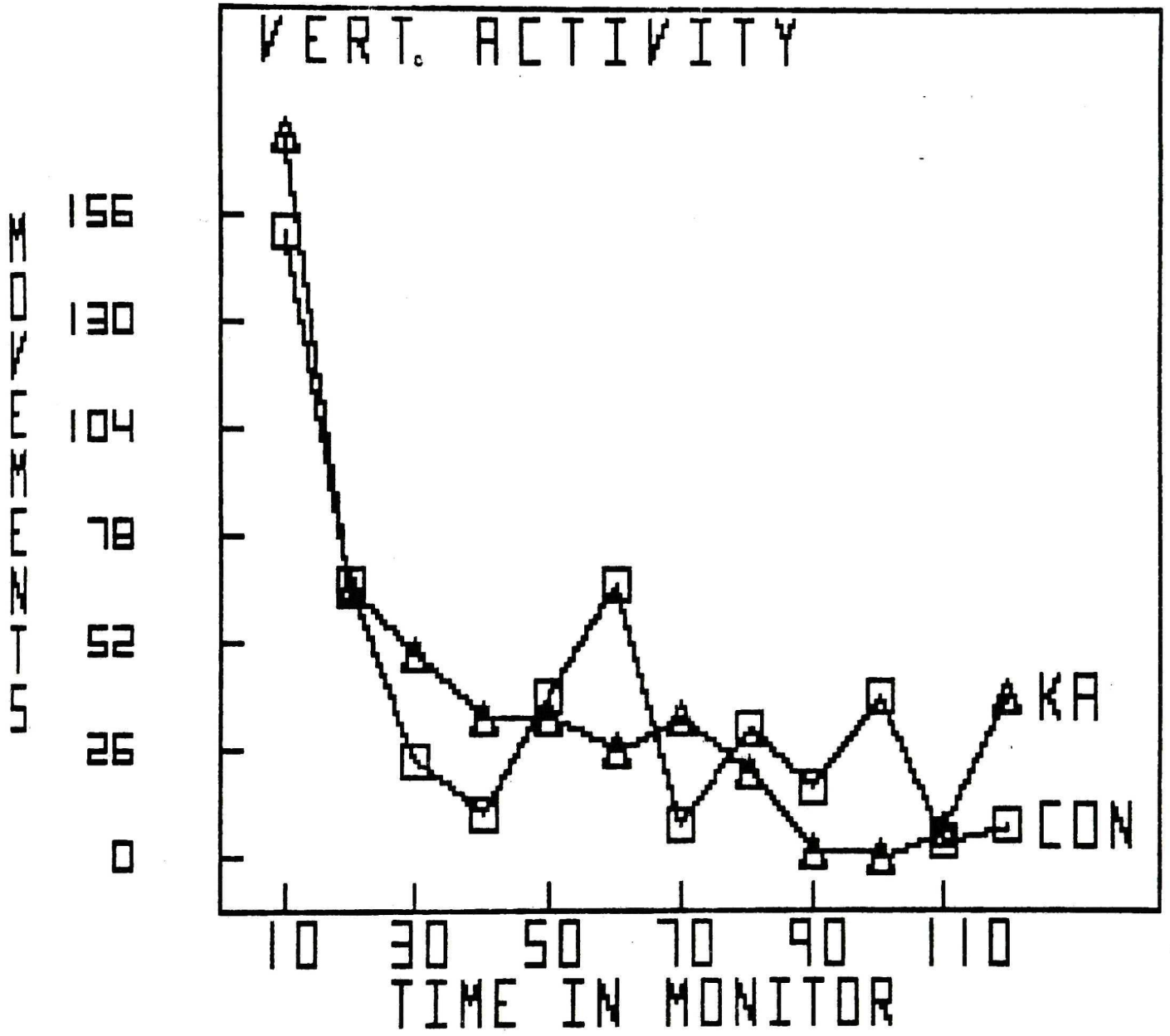
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	128.391	1	128.391	.003	
ERROR	433084.969	14	30934.641		
WITHIN SUBJECTS					
TIME IN MONITOR	2864298.28	11	260390.753	21.623	<.001
LESION X TIME	65891.781	11	5990.162	.497	
ERROR	1854537.640	154	12042.452		



This graph displays the mean number of seconds spent resting by the 2 groups of animals during the 120 minutes they were in the animal activity monitor. Squares represent sham lesioned controls; triangles represent the kainic acid lesioned group.

VERTICAL ACTIVITY ANOVA

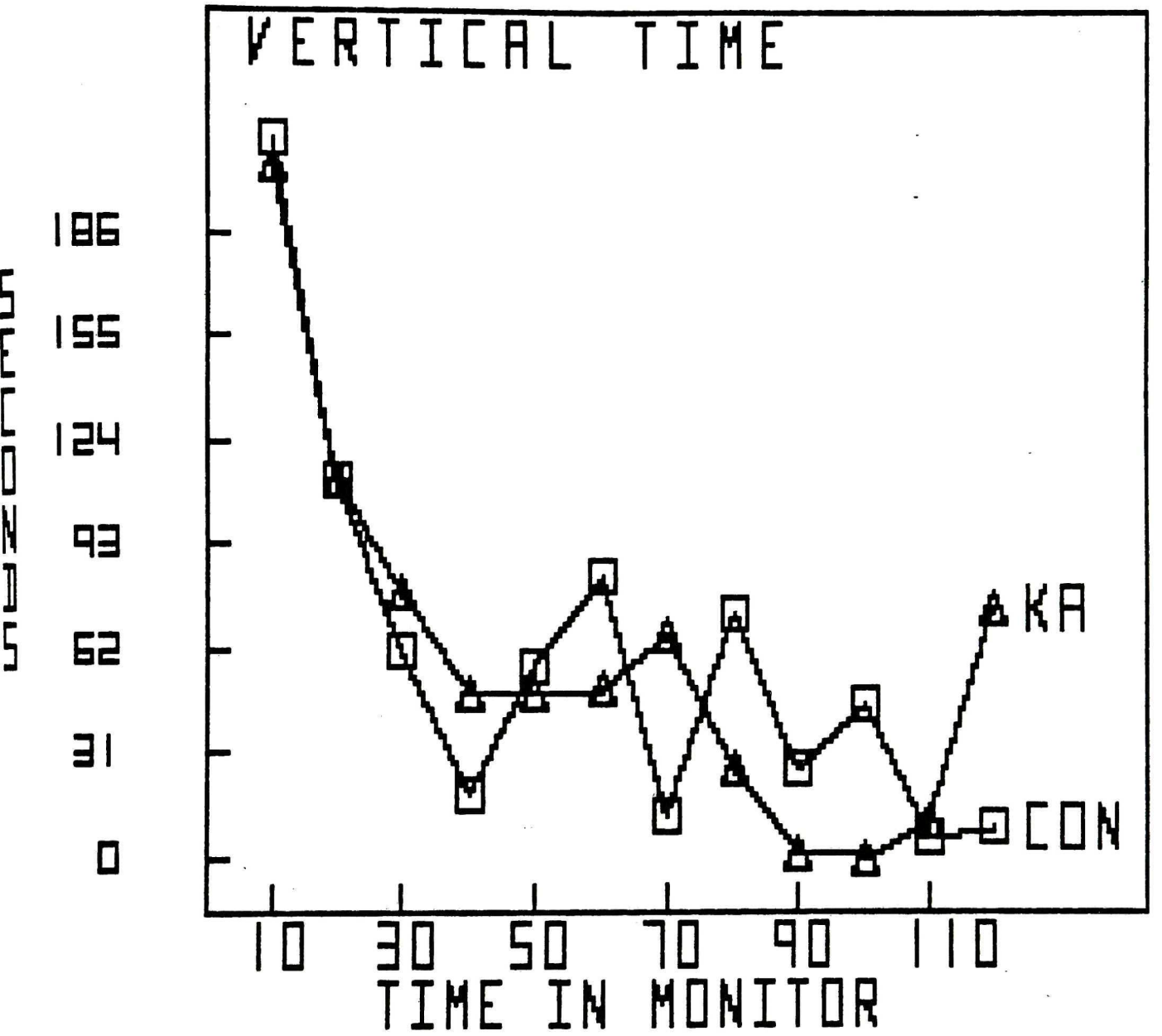
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	135.005	1	135.005	.004	
ERROR	362773.615	14	25912.401		
WITHIN SUBJECTS					
TIME IN MONITOR	318755.766	11	28977.797	8.881	<.001
LESION X TIME	27399.057	11	2490.823	.763	
ERROR	502475.760	154	3262.830		



Mean number of movements per group for each 10 minute time interval is plotted over the 2 hours the animals were in the activity monitor. Squares represent sham lesioned controls; triangles are kainic acid lesioned rats.

VERTICAL TIME ANOVA

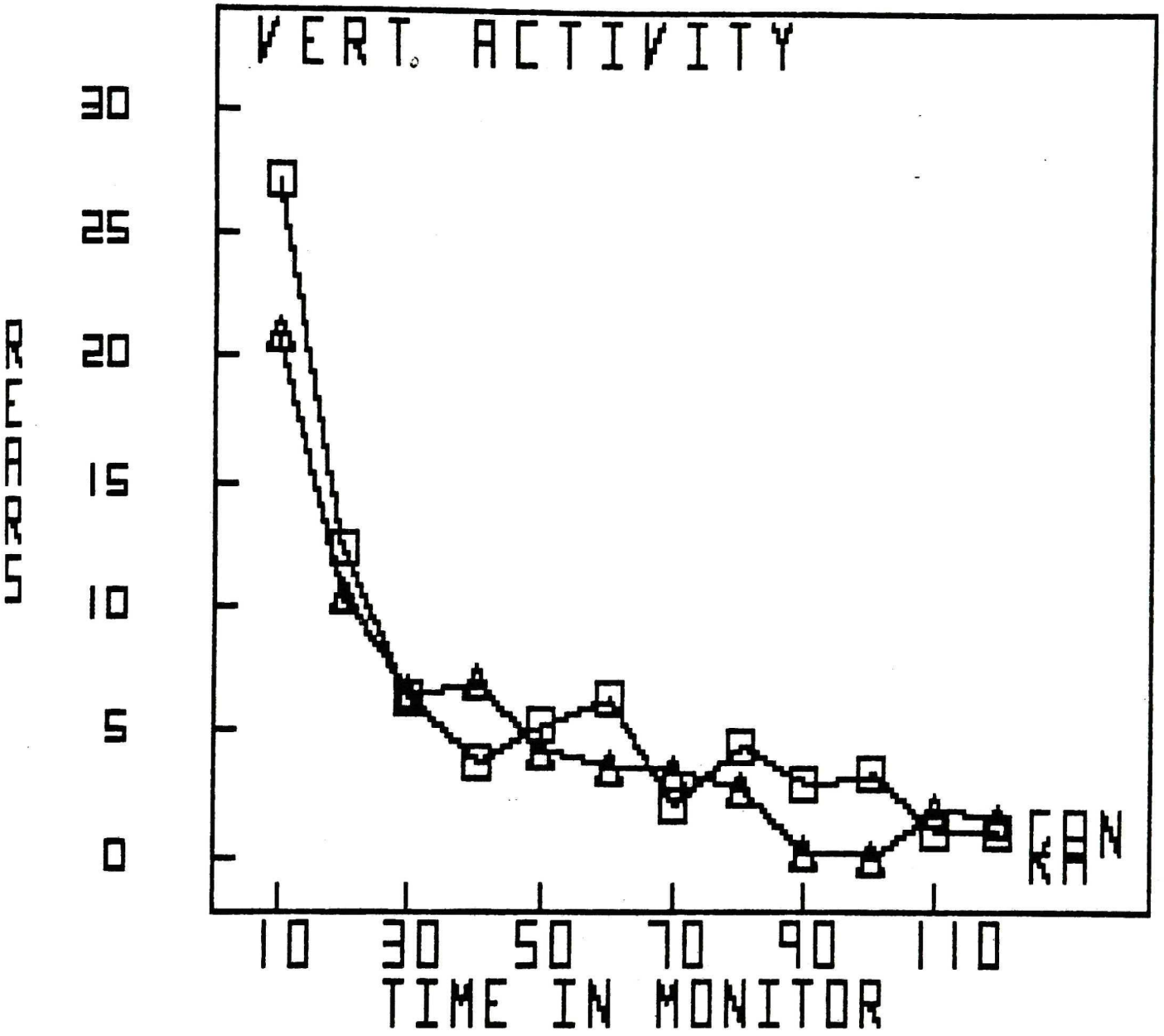
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	23.380	1	23.380	.000	
ERROR	1172947.700	14	83781.979		
WITHIN SUBJECTS					
TIME IN MONITOR	532092.558	11	48372.051	5.580	<.001
LESION X TIME	58381.682	11	5307.426	.612	
ERROR	1334999.680	154	8668.829		



Mean number of seconds of vertical activity accrued by each group of animals during the 12, 10 minute periods they spent in the activity monitor. Squares represent sham lesioned controls; triangles are kainic acid lesioned only rats.

VERTICAL REARS ANOVA

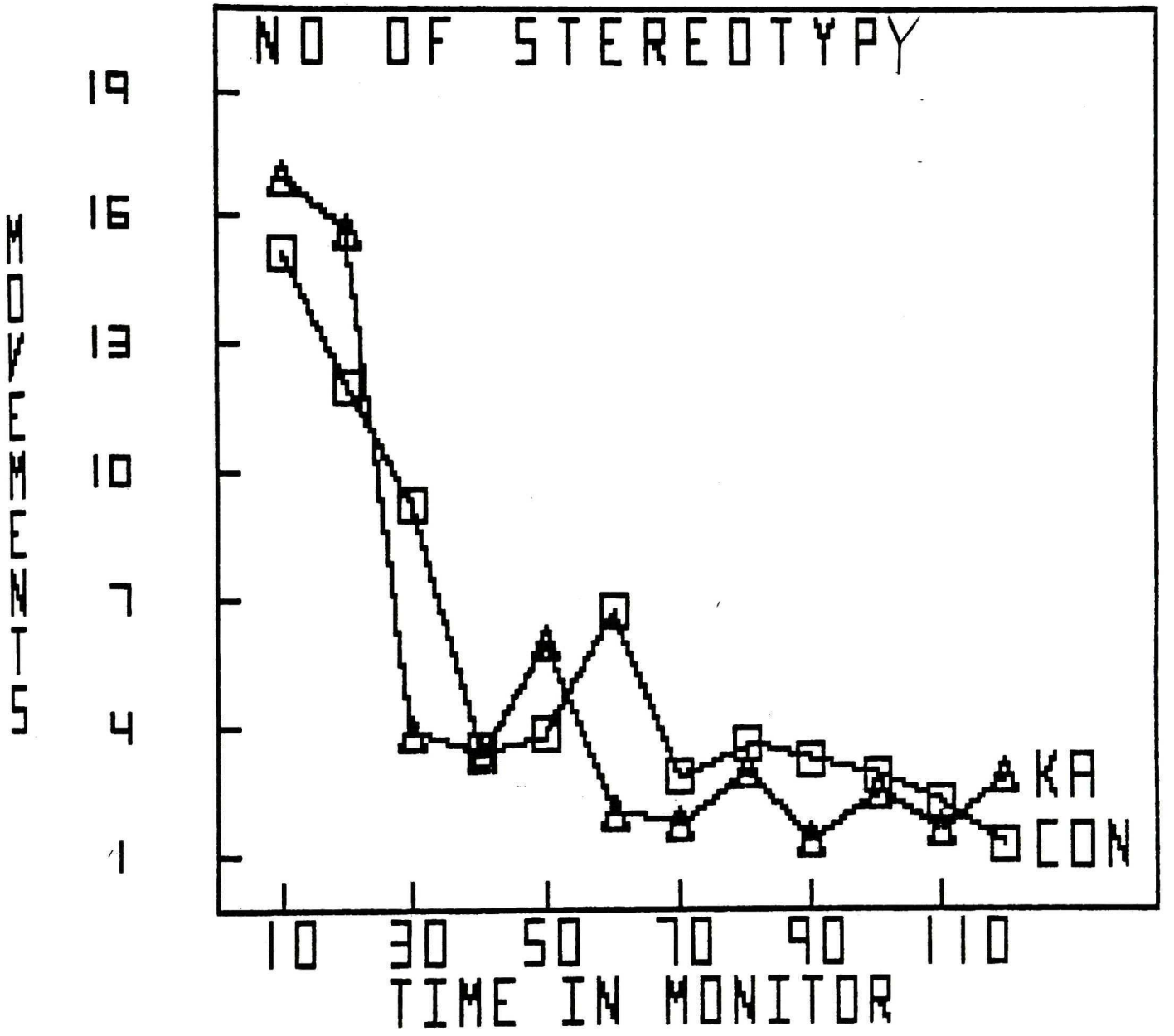
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	63.021	1	63.021	.286	
ERROR	3085.792	14	220.414		
WITHIN SUBJECTS					
TIME IN MONITOR	7352.854	11	668.441	19.129	<.001
LESION X TIME	279.854	11	25.441	.728	
ERROR	5381.458	154	34.945		



Mean number of rears, plotted for each of the 10 minutes that animals were in the activity monitor, is displayed. Sham lesioned animals are represented by squares; kainic acid lesioned by triangles.

NUMBER OF STEREOTYPIC MOVEMENTS ANOVA

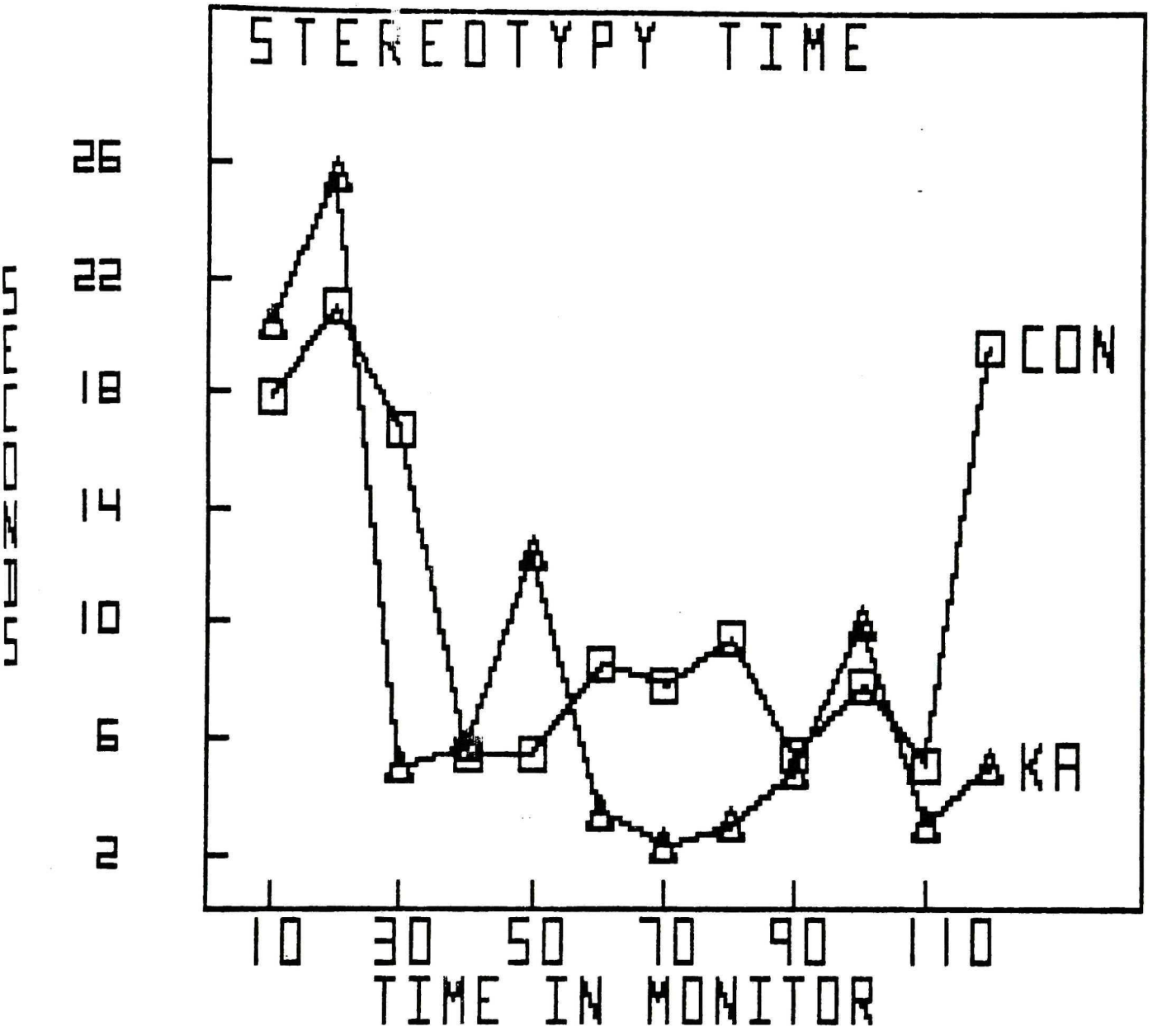
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	11.021	1	11.021	.315	
ERROR	490.396	14	35.028		
WITHIN SUBJECTS					
TIME IN MONITOR	3894.625	11	354.057	16.046	<.001
LESION X TIME	311.104	11	28.282	1.282	.239
ERROR	3398.104	154	22.066		



Mean number of stereotypic movements for each group of animals, plotted at 10 minute time interval over the course of 2 hours. Squares are sham lesioned controls; triangles represent kainic acid lesioned rats.

STEREOTYPY TIME

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	285.188	1	285.188	.805	
ERROR	4961.292	14	354.378		
WITHIN SUBJECTS					
TIME IN MONITOR	6446.438	11	586.040	2.212	.016
LESION X TIME	1853.188	11	168.472	.636	
ERROR	40803.208	154	264.956		

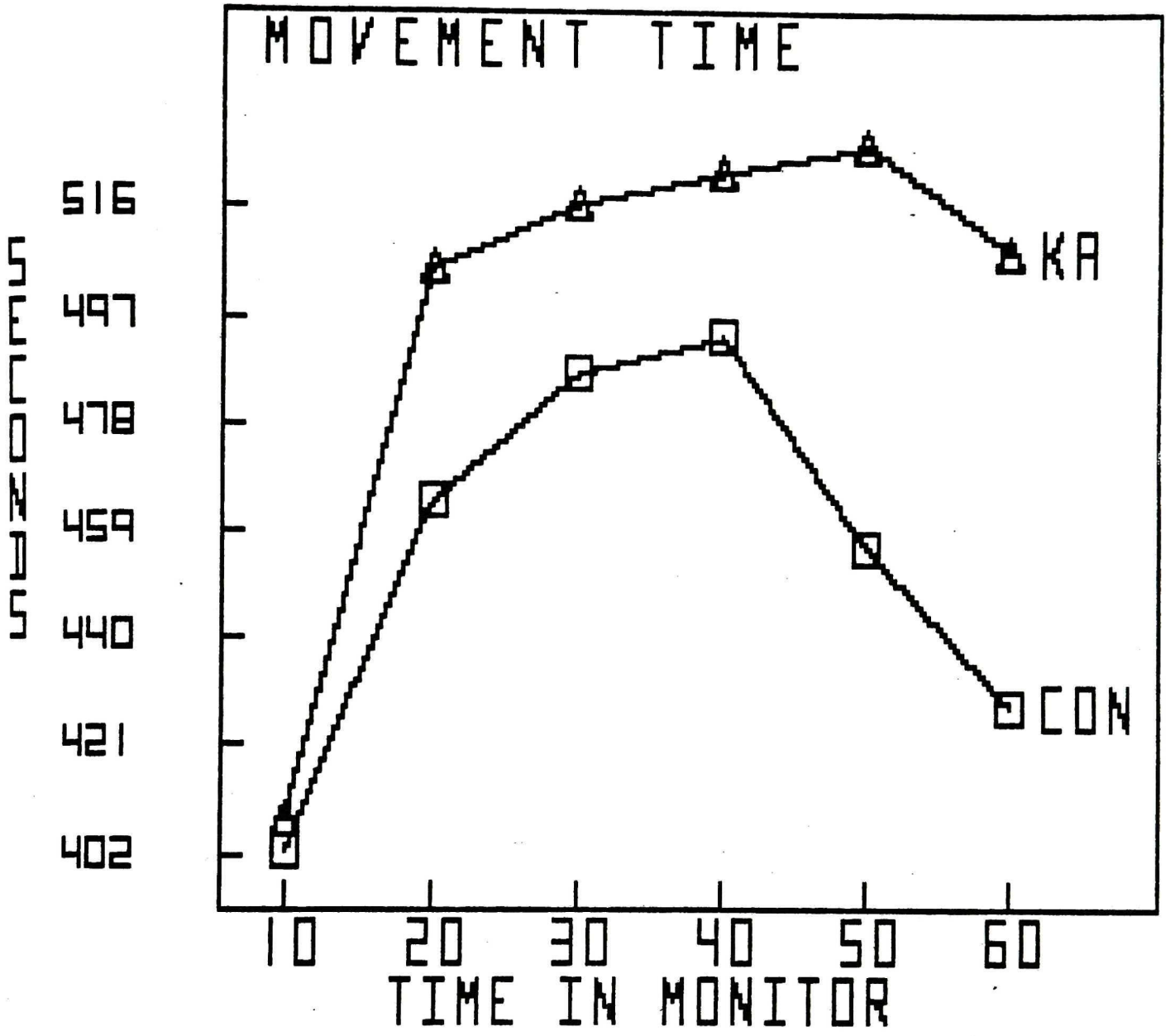


Mean number of seconds of stereotypic movements, plotted for each 10 minute time interval the animals were in the monitor. Squares represent sham lesioned controls; triangles are the kainic acid lesioned group.

APPENDIX D

MOVEMENT TIME AFTER AMPHETAMINE ADMINISTRATION
(UNWEIGHTED-MEANS SOLUTION)

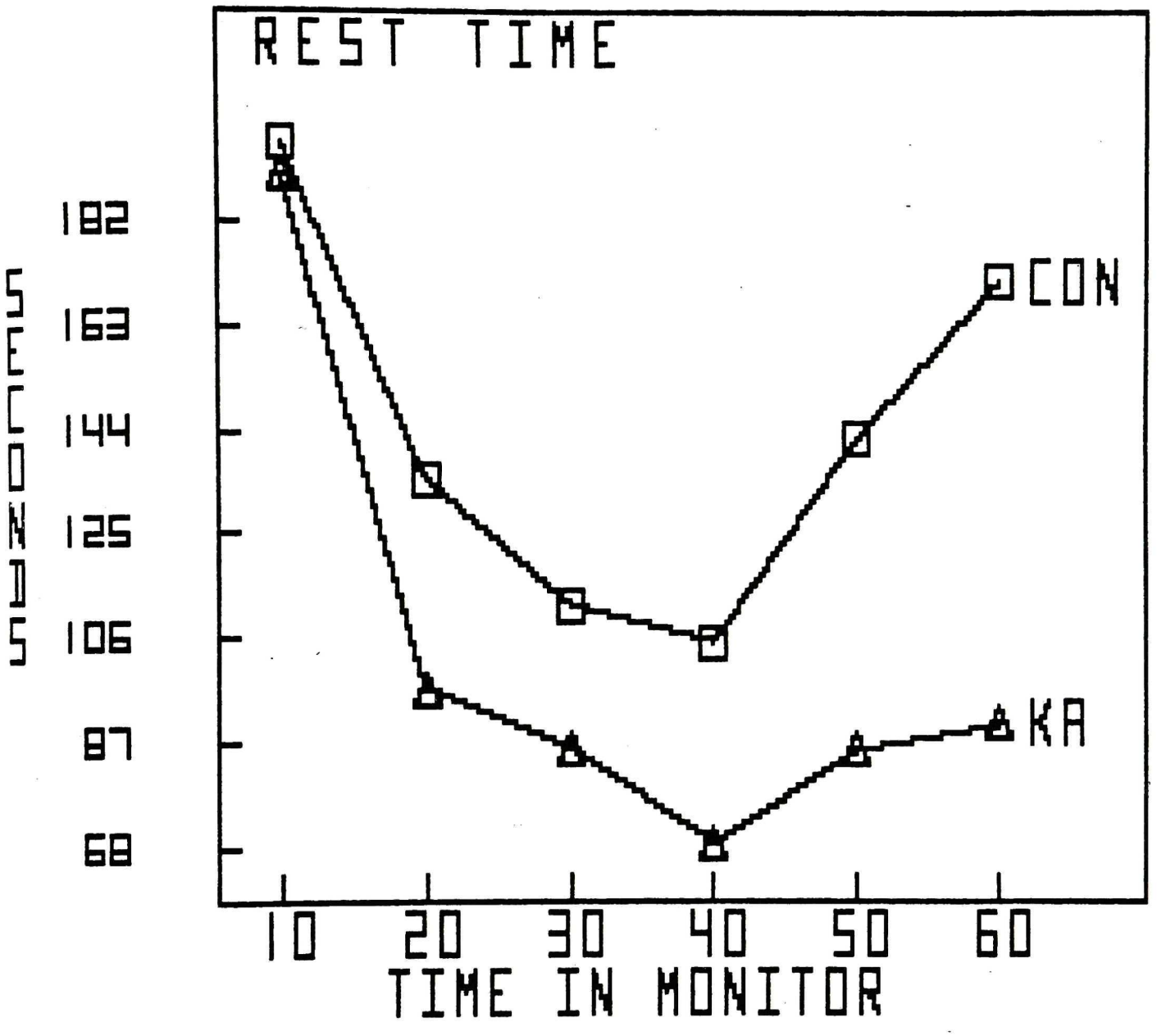
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	41779.588	1	41799.588	1.883	.191
ERROR	288513.148	13	22193.319		
WITHIN SUBJECTS					
TIME IN MONITOR	106269.005	5	21253.801	4.601	<.001
LESION X TIME	14692.876	5	2938.575	.636	
ERROR	300278.246	65	4619.665		



Mean number of seconds spent moving by the 2 groups of animals during the 60 minutes they were in the activity monitor after injection with d-amphetamine. Squares are sham lesioned controls; triangles represent the kainic acid lesioned group.

REST TIME AFTER AMPHETAMINE INJECTION
(UNWEIGHTED-MEANS SOLUTION)

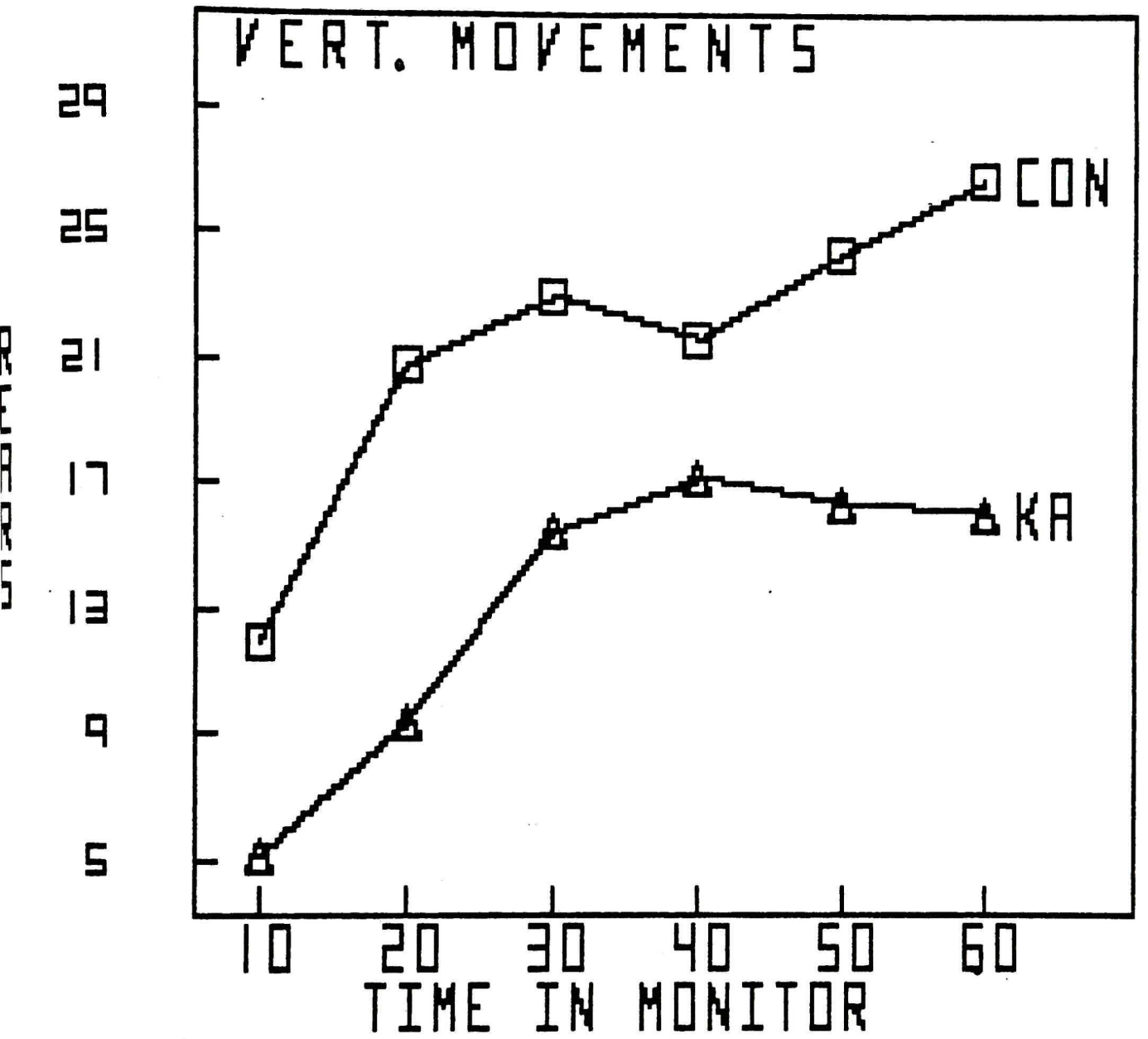
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	37250.953	1	37250.953	1.705	.212
ERROR	284095.536	13	21853.503		
WITHIN SUBJECTS					
TIME IN MONITOR	105327.107	5	21065.422	4.487	<.001
LESION X TIME	12392.442	5	2478.488	.528	
ERROR	305166.534	65	4694.870		



This graph displays the mean number of seconds spent resting by the 2 groups of animals during the 60 minutes after amphetamine injection. Squares represent sham lesioned controls; tringles represent kainic acid lesioned.

REARING ACTIVITY AFTER AMPHETAMINE INJECTION
(UNWEIGHTED-MEANS SOLUTION)

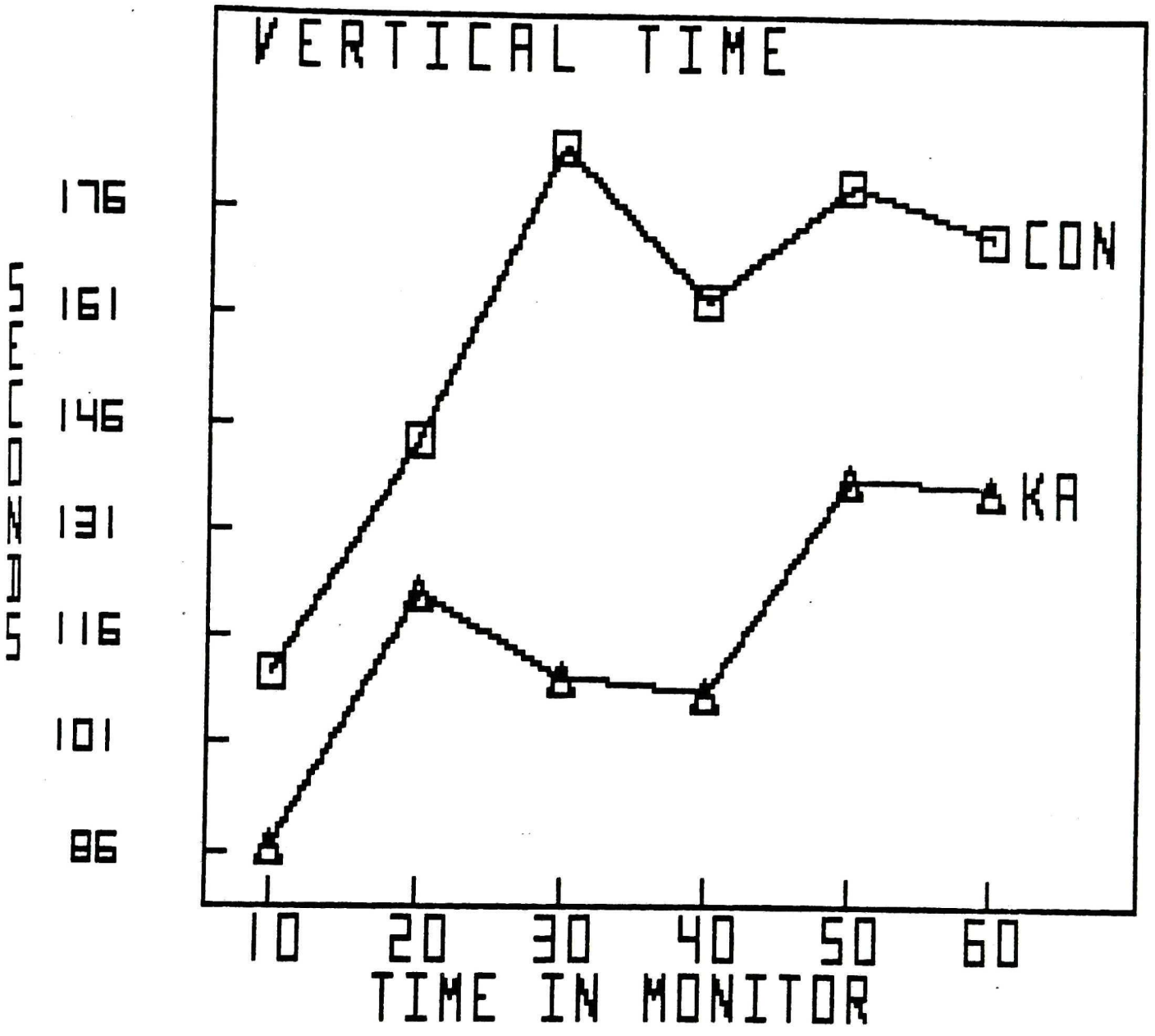
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	1490.691	1	1490.691	2.172	.161
ERROR	8921.265	13	686.251		
WITHIN SUBJECTS					
TIME IN MONITOR	1731.735	5	346.347	3.805	.004
LESION X TIME	121.780	5	24.356	.268	
ERROR	5916.932	65	91.030		



Mean number of rears, plotted for each of the 10 minutes that animals were in the activity monitor, is displayed. Sham lesioned animals are represented by squares; kainic acid lesioned by triangles.

VERTICAL TIME AFTER AMPHETAMINE ADMINISTRATION
(UNWEIGHTED-MEANS SOLUTION)

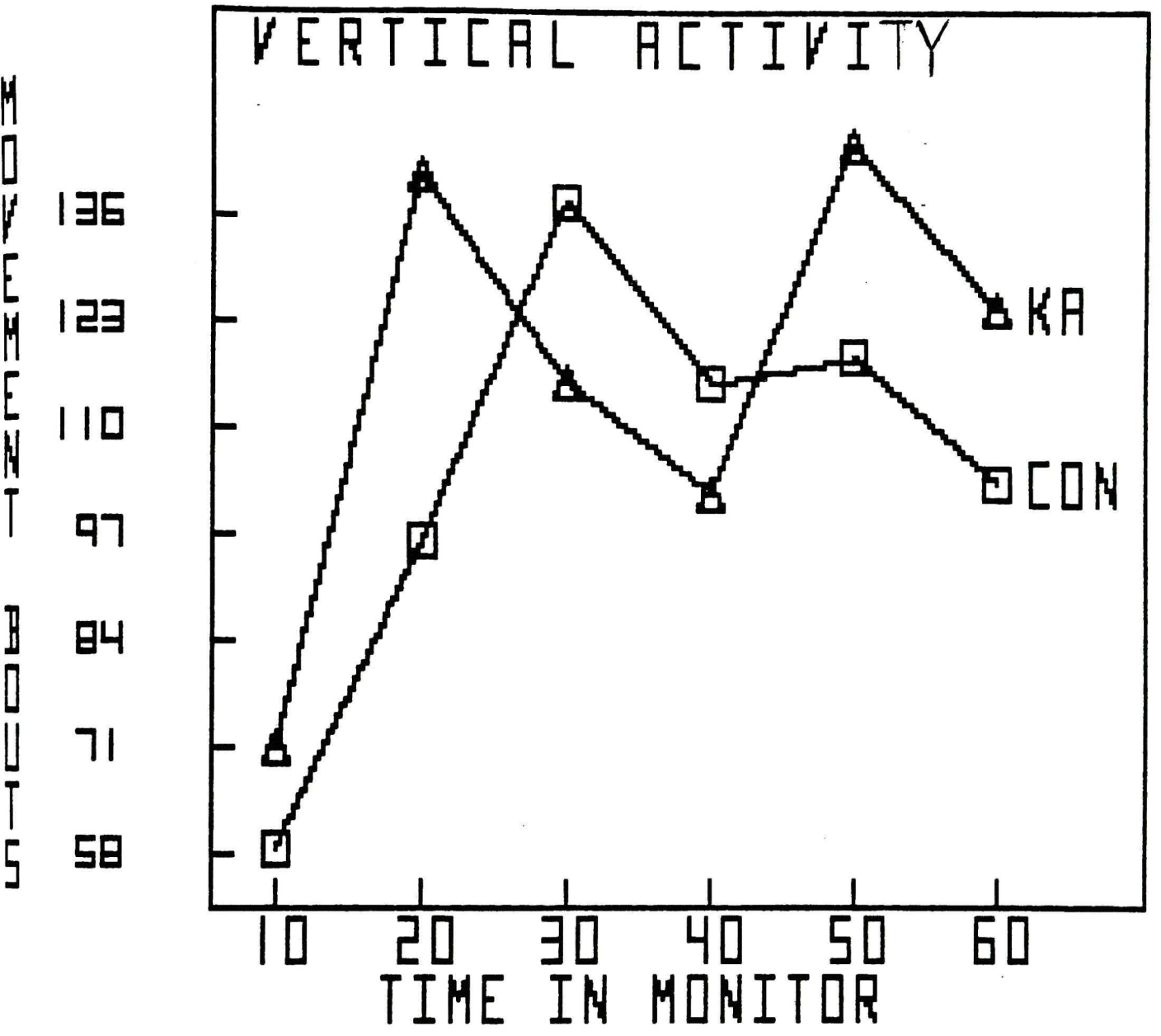
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	39732.303	1	39732.303	.277	
ERROR	1863406.440	13	143338.957		
WITHIN SUBJECTS					
TIME IN MONITOR	35652.170	5	7130.434	1.888	.107
LESION X TIME	7433.854	5	1486.771	.394	
ERROR	245455.935	65	3776.245		



Mean number of seconds of vertical activity by each group of animals during the 6, 10 minute time interveals they spent in the monitor after being injected with d-amphetamine. Squares are sham lesioned controls; triangles are kainic acid lesioned rats.

VERTICAL ACTIVITY AFTER INJECTION WITH AMPHETAMINE
(UNWEIGHTED-MEANS SOLUTION)

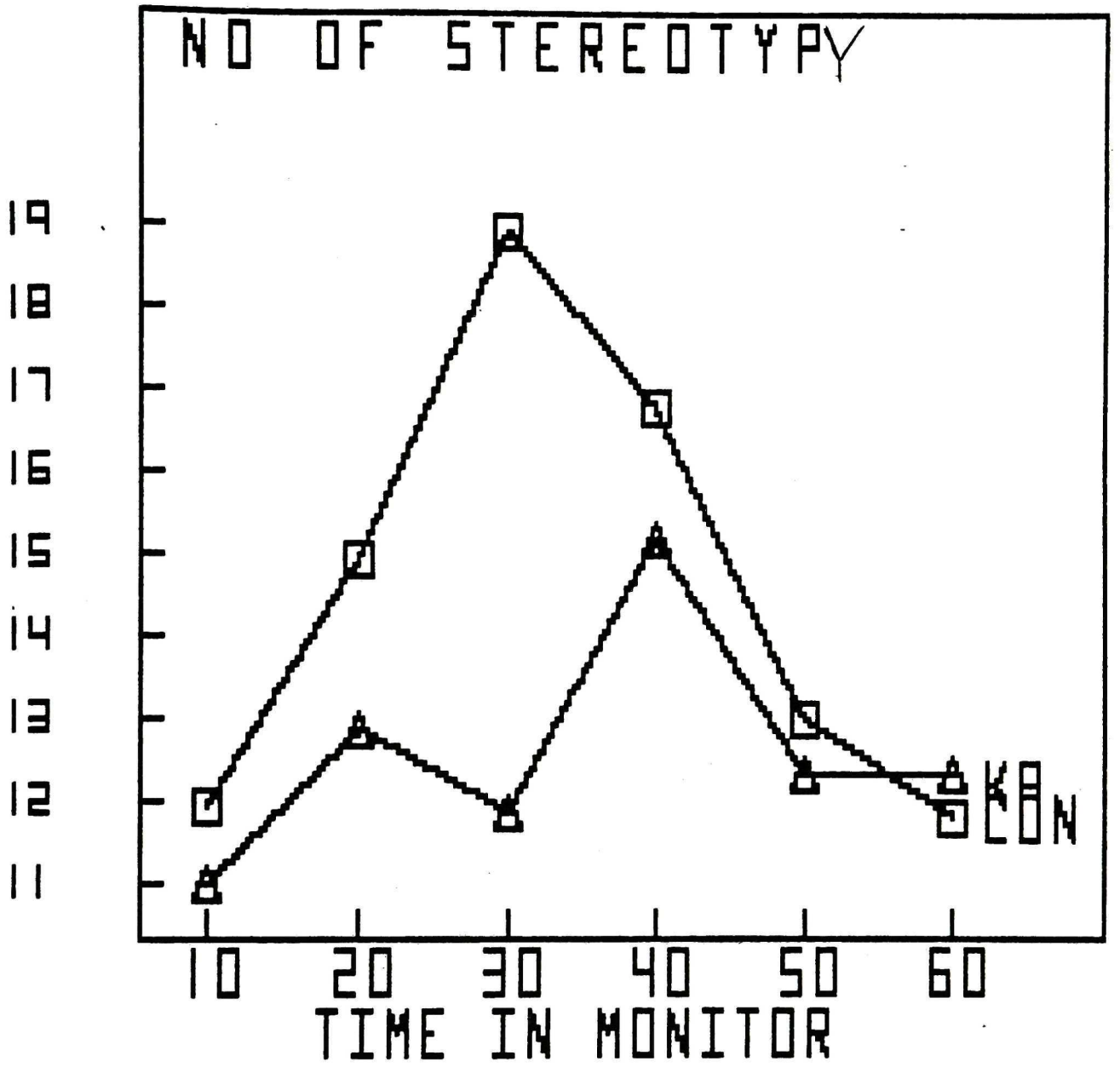
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	2947.085	1	2947.085	.029	
ERROR	1329505.540	13	102269.657		
WITHIN SUBJECTS					
TIME IN MONITOR	43457.017	5	8691.403	1.901	.105
LESION X TIME	11890.619	5	2378.124	.520	
ERROR	297230.884	65	4572.783		



Mean number of vertical movements per group for each 10 minute time interveal is plotted over the 60 minutes that animals were in the activity monitor after being injected with d-amphetamine. Squares are sham lesioned controls; triangles are kainic acid lesioned.

NUMBER OF STEREOTYPIC MOVEMENTS AFTER AMPHETAMINE INJECTION
(UNWEIGHTED-MEANS SOLUTION)

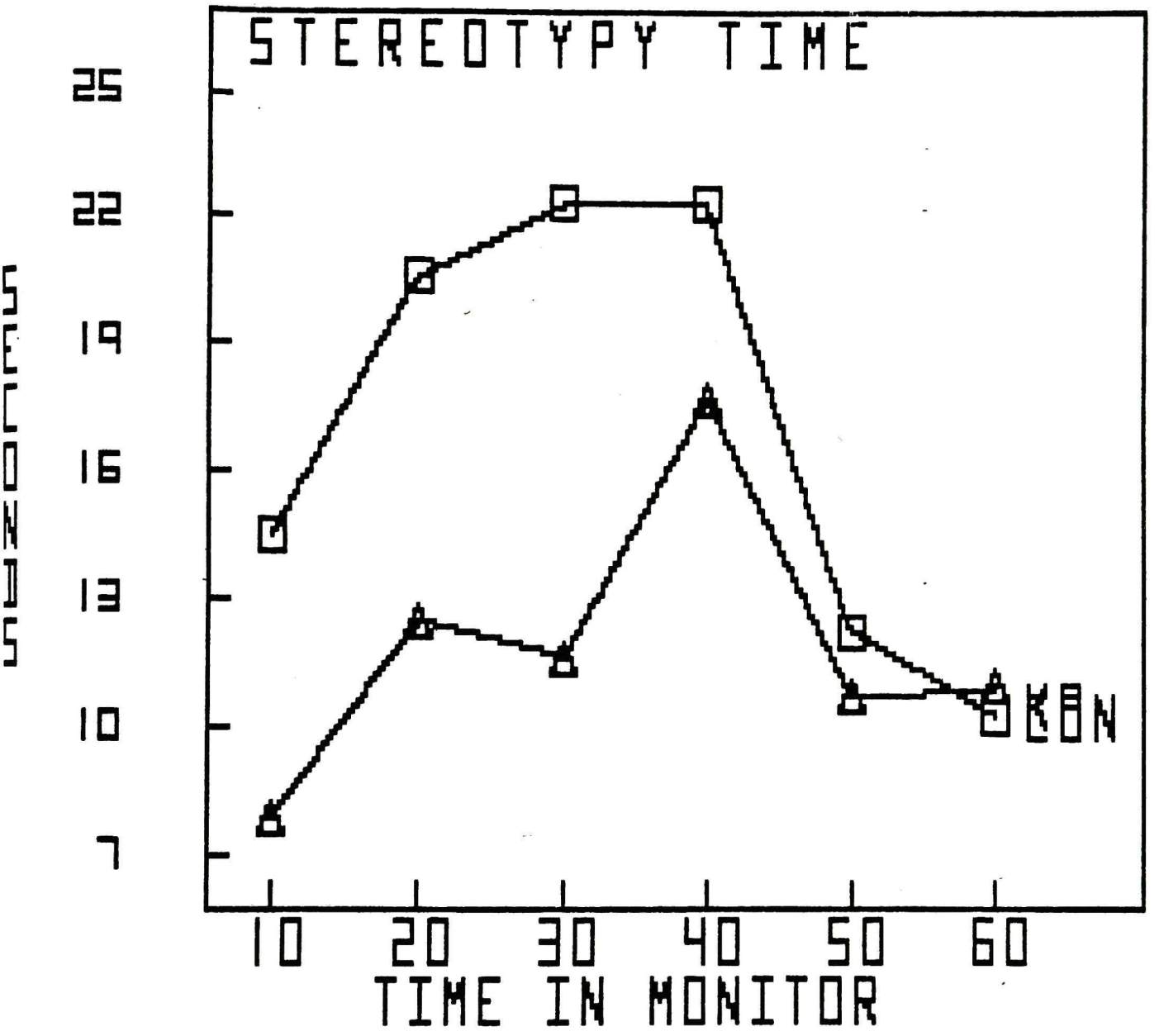
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	85.124	1	85.124	.713	
ERROR	1553.098	13	119.469		
WITHIN SUBJECTS					
TIME IN MONITOR	250.489	5	50.098	2.200	.064
LESION X TIME	129.422	5	25.884	1.137	.349
ERROR	1479.955	65	22.769		



Mean number of stereotypic movements for each group of animals, plotted at 10 minute time interveals over the course of 60 minutes after injection with d-amphetamine. Squares are sham lesioned; triangles are kainic acid lesioned.

STEREOTYPY TIME AFTER AMPHETAMINE
(UNWEIGHTED-MEANS SOLUTION)

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	601.405	1	601.405	.918	
ERROR	8518.884	13	655.299		
WITHIN SUBJECTS					
TIME IN MONITOR	1136.694	5	227.339	1.968	.094
LESION X TIME	341.894	5	68.379	.592	
ERROR	7506.884	65	115.491		

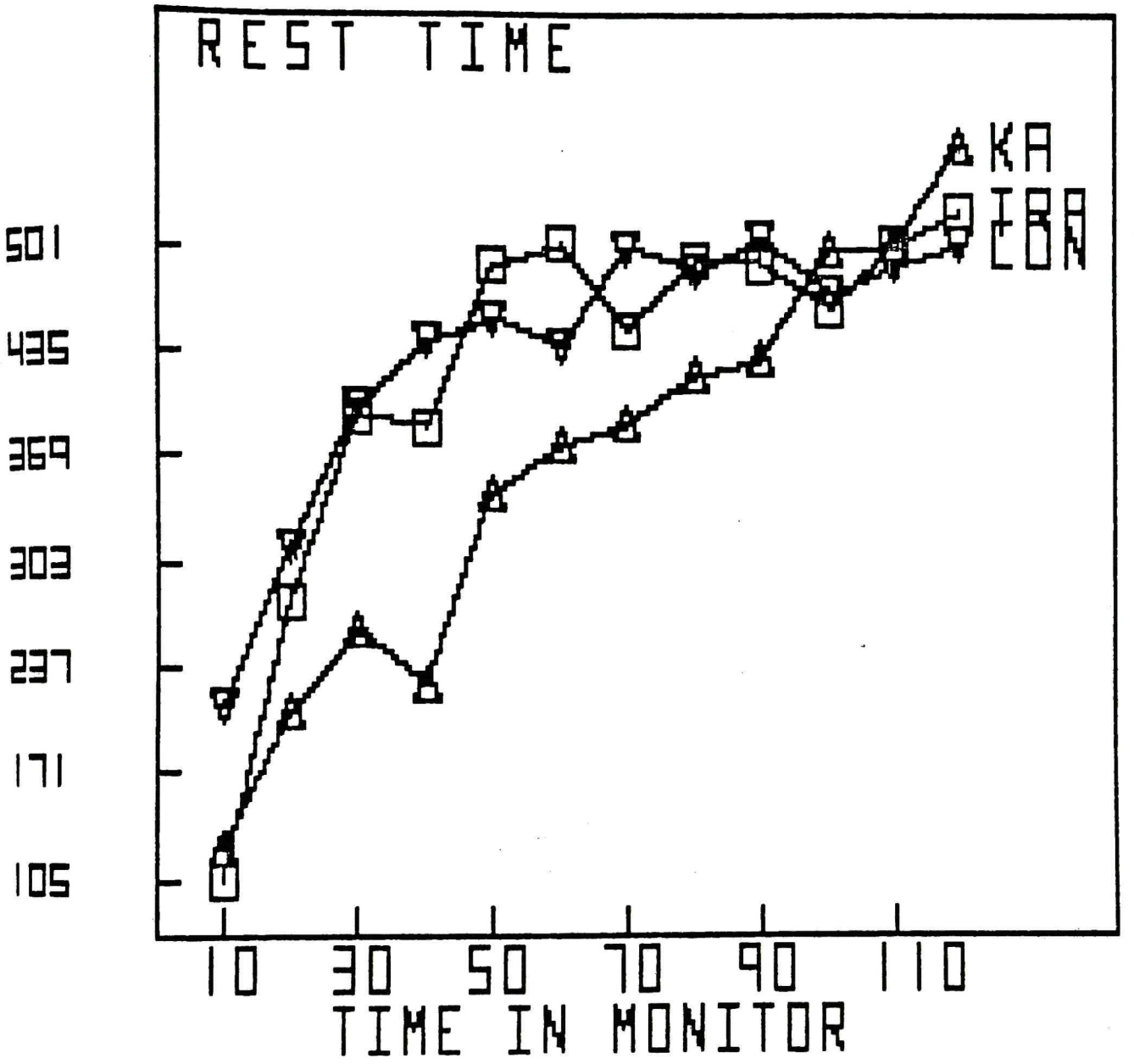


Mean number of seconds of stereotypic movements, plotted for each 10 minute time interveal the animals were in the monitor after administration of d-amphetamine. Squares represent sham lesioned controls; triangles represent the kainic acid lesioned group.

APPENDIX E

REST TIME

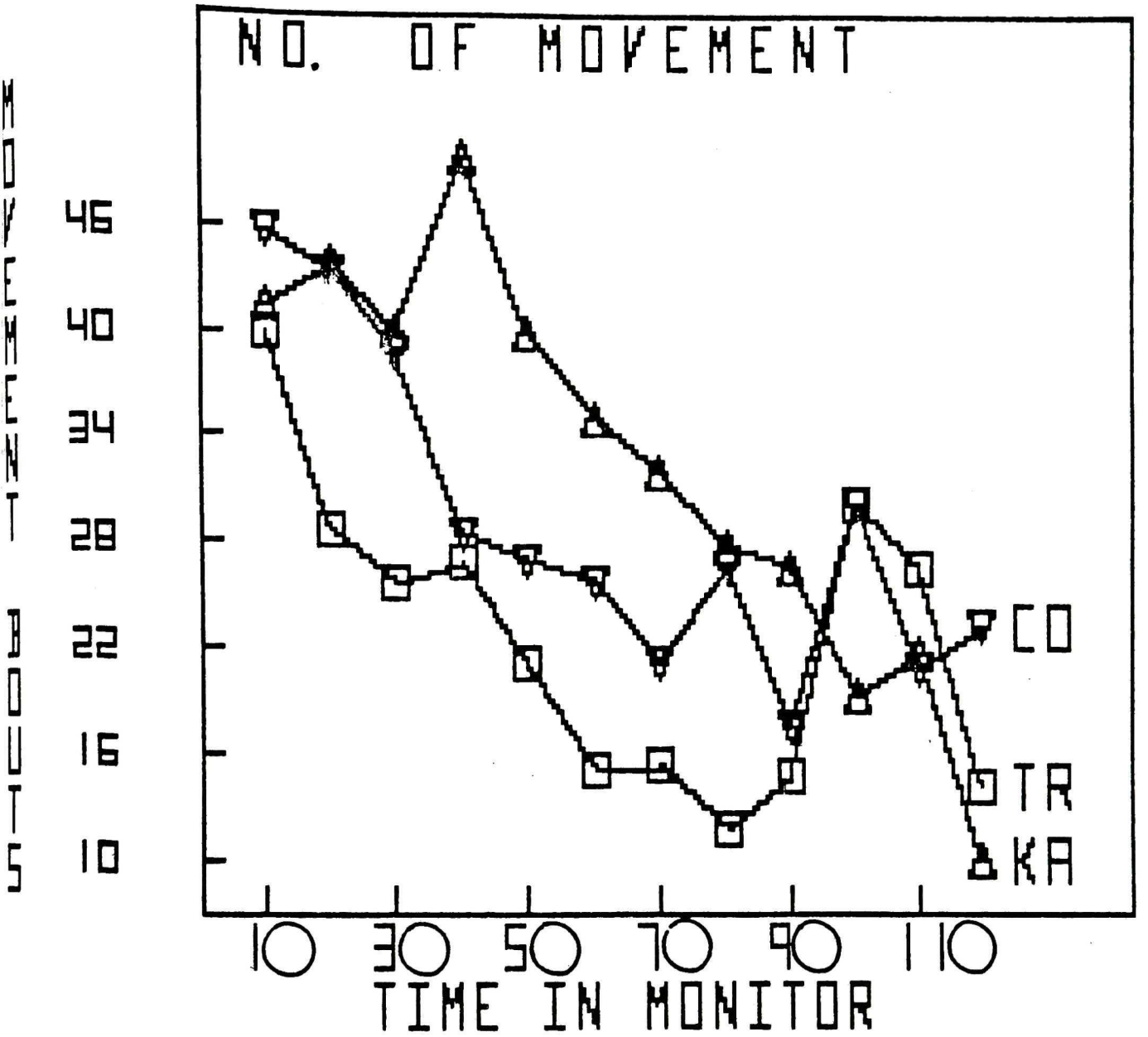
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	241711.792	2	120855.896	.911	
ERROR	2254554.810	17	132620.871		
WITHIN SUBJECTS					
TIME IN MONITOR	2664088.730	11	242189.885	20.266	.001
LESION X TIME	322096.618	22	14640.755	1.225	.230
ERROR	2234716.220	187	11950.354		



Mean number of seconds spent resting by the 3 groups of animals during the 120 minutes they were in the animal activity monitor. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls.

NUMBER OF MOVEMENTS

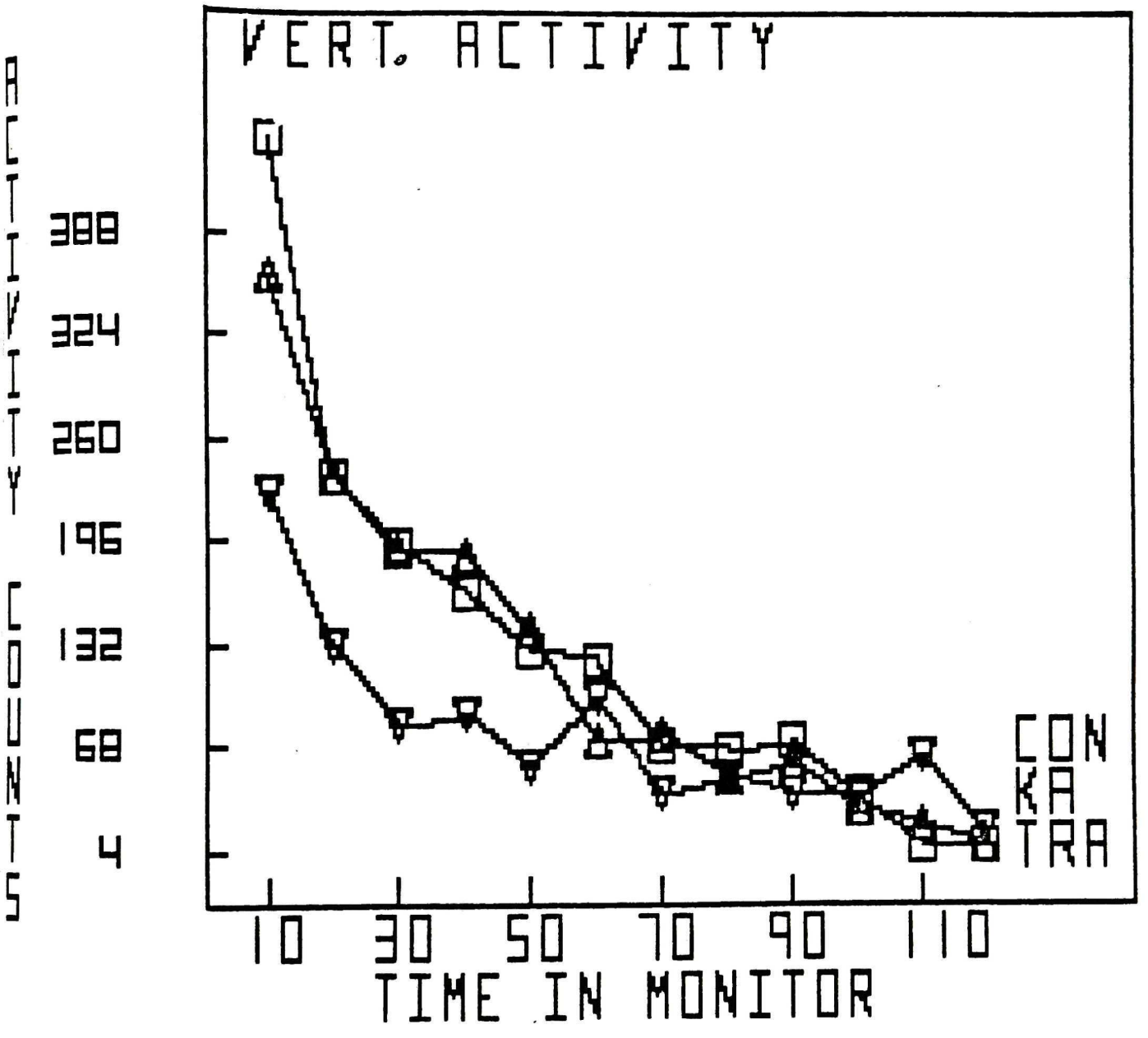
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	3973.831	2	1986.916	.938	
ERROR	35993.593	17	2117.270		
WITHIN SUBJECTS					
TIME IN MONITOR	14555.738	11	1323.249	5.616	.001
LESION X TIME	6528.532	22	296.751	1.259	.204
ERROR	44061.241	187	235.622		



Mean number of seconds spent moving by the 3 groups of animals during the 120 minutes they were in the animal activity monitor. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls.

VERTICAL ACTIVITY

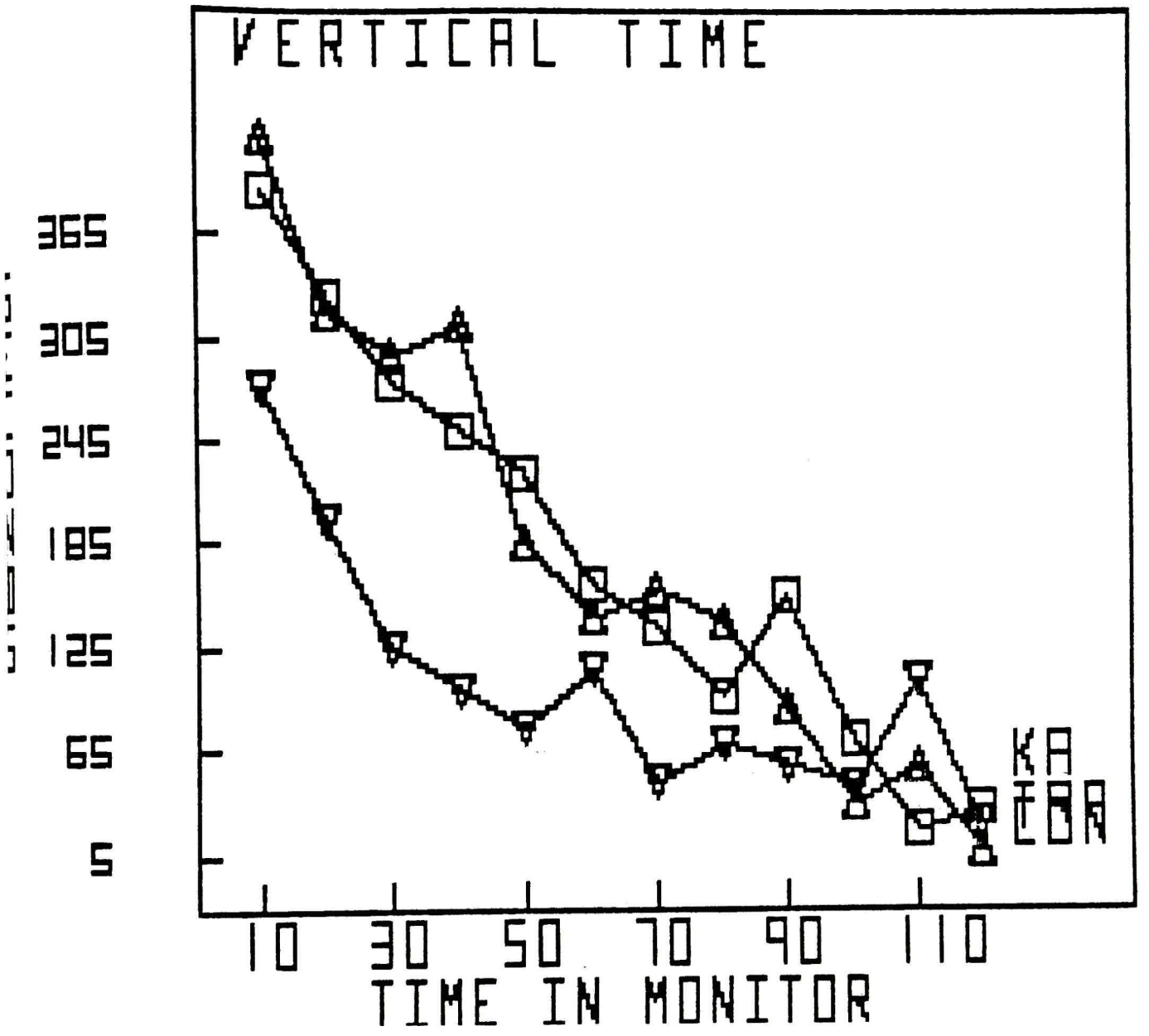
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	1199553.906	2	59776.953	.752	
ERROR	1350776.670	17	79457.451		
WITHIN SUBJECTS					
TIME IN MONITOR	1945201.440	11	176836.495	19.470	.001
LESION X TIME	240615.053	22	10937.048	1.204	.248
ERROR	1698446.980	187	9082.604		



Mean number of vertical activity counts, plotted for each of the 10 minutes that animals were in the activity monitor. Squares are implanted animals, upward pointing triangles are lesioned, and downward pointing are controls.

VERTICAL TIME

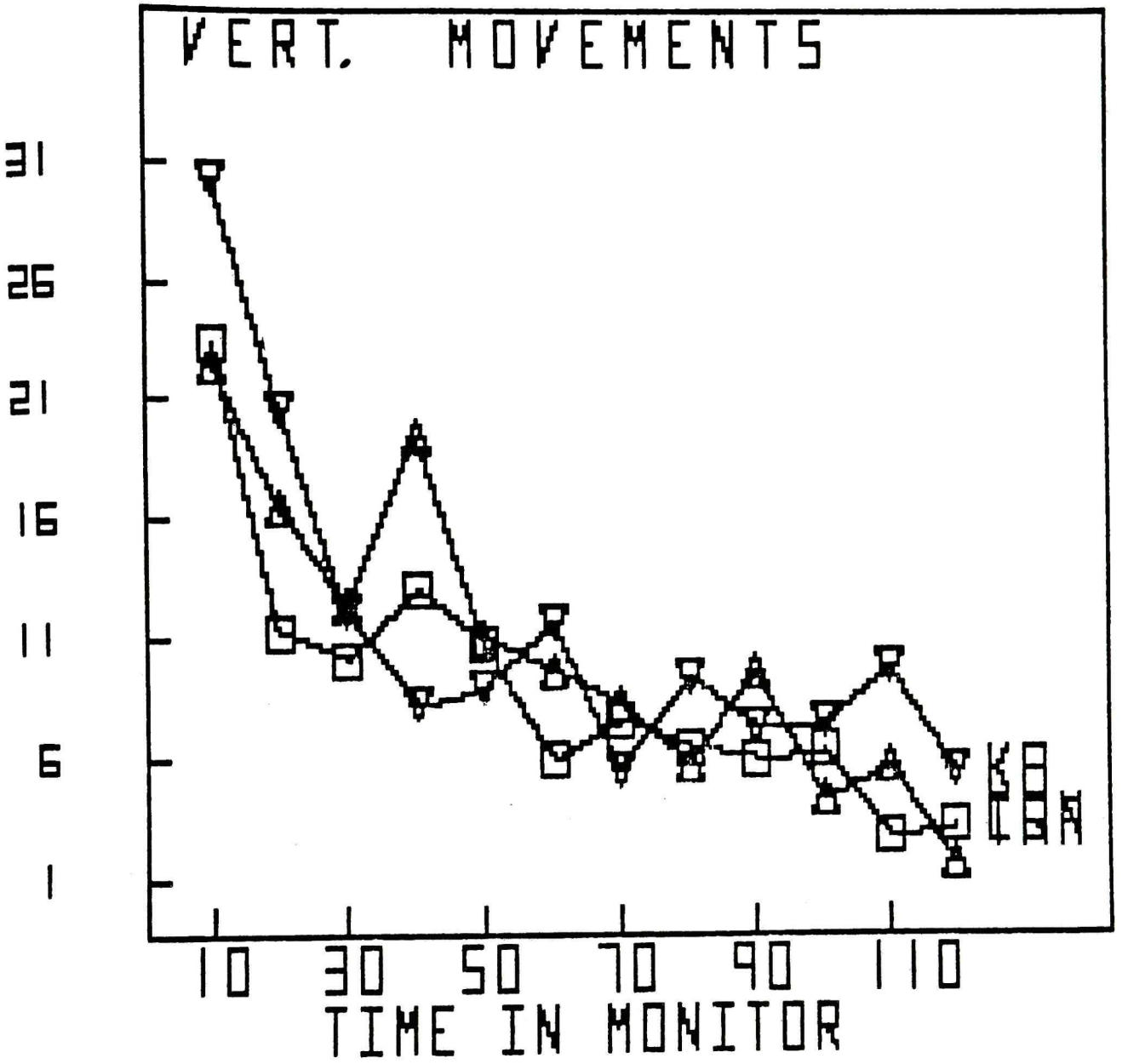
SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	315347.457	2	157673.728		.847
ERROR	3163876.150	17	186110.362		
WITHIN SUBJECTS					
TIME IN MONITOR	2308352.160	11	209850.197	15.909	.001
LESION X TIME	330056.073	22	15002.549	1.137	.310
ERROR	2466712.730	187	13190.977		



Mean number of seconds of vertical activity by each group of animals over the 12, 10 minute periods they spent in the activity monitor. Squares represent implanted, upward pointing are lesioned only, and downward pointing are controls.

VERTICAL MOVEMENTS

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	268.276	2	134.138	.188	
ERROR	12100.316	17	711.783		
WITHIN SUBJECTS					
TIME IN MONITOR	7680.985	11	698.271	8.917	.001
LESION X TIME	1233.471	22	56.067	.716	
ERROR	14643.804	187	78.309		

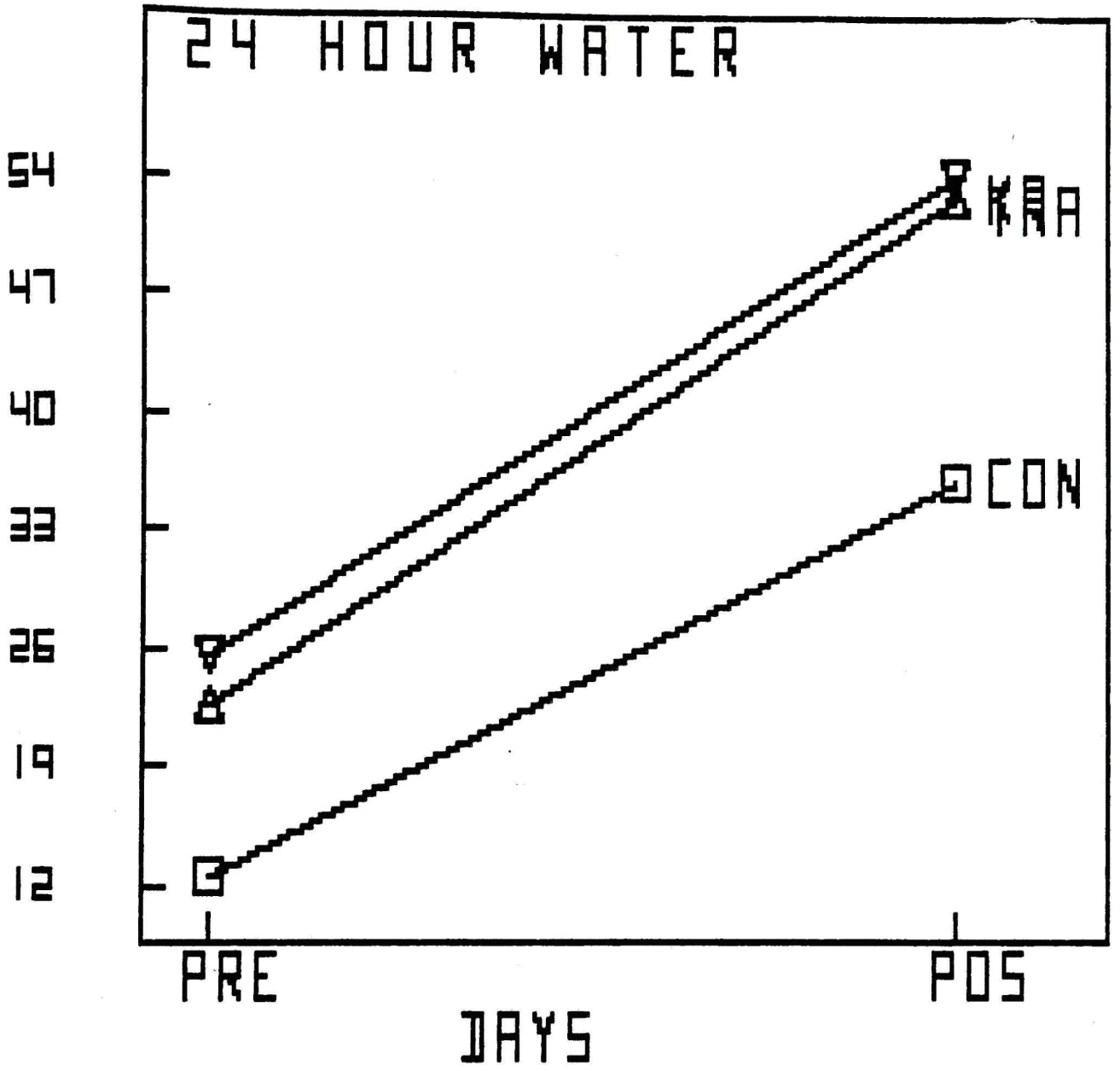


Mean number of vertical movements per group for each 10 minute time interval is plotted over the 2 hours the animals were in the activity monitor. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls.

APPENDIX F

24 HOUR FOOD CONSUMPTION BEFORE, DURING, AND AFTER INSULIN INJECTION.

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	104.672	2	52.336	.860	
ERROR	486.628	8	60.828		
WITHIN SUBJECTS					
24 HR FOOD CONSUM.	39.696	2	19.848	.735	
LESION X 24 HR FOOD CONSUM.	78.946	4	19.736	.731	
ERROR	486.149	18	27.008		



Mean 24 hour water consumption on the day of, and the day after, 24 hours of food deprivation. Downward pointing triangles are implanted, upward pointing triagles are lesioned only, and squares are controls.

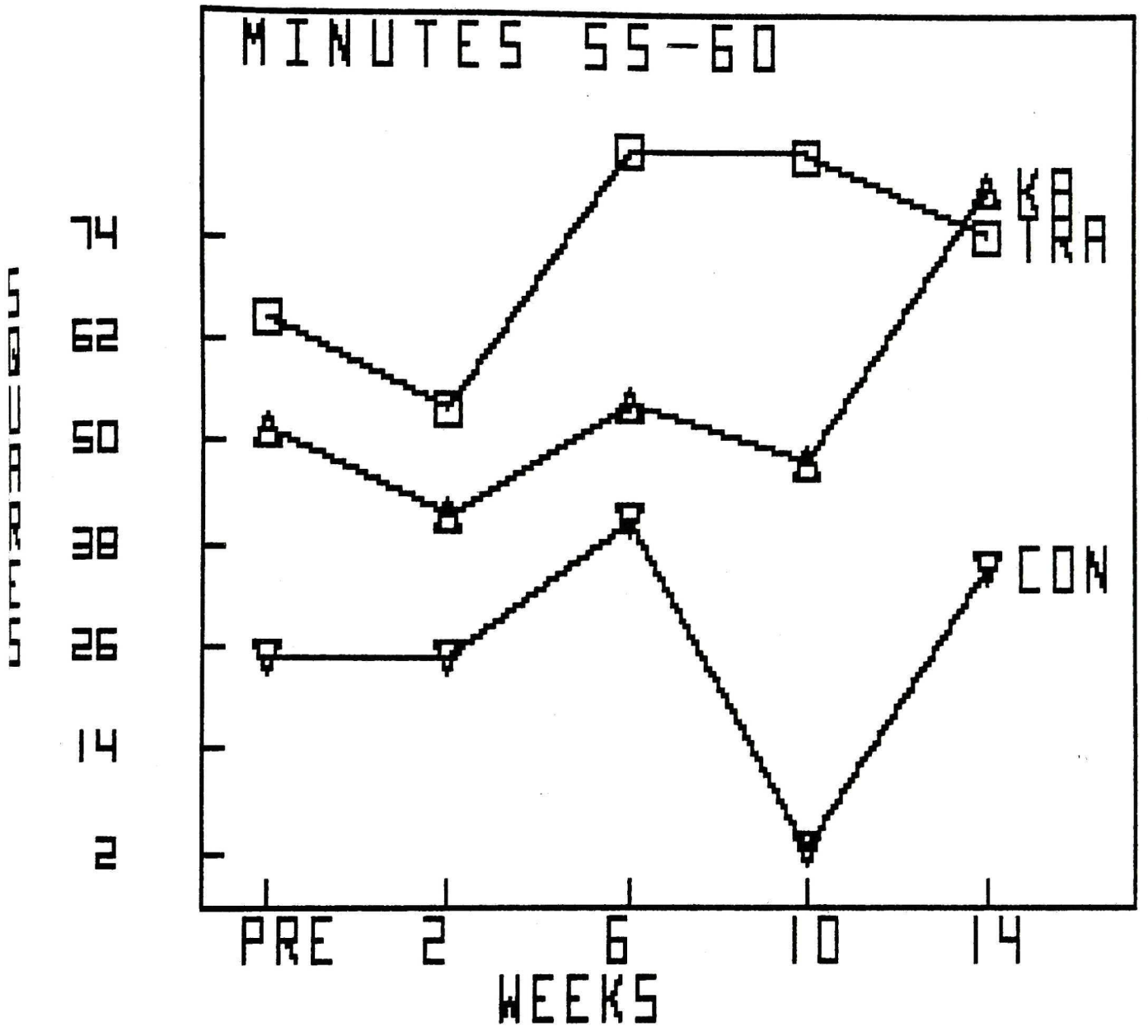
WATER CONSUMPTION, PRE AND POST FOOD DEPRIVATION.

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	898.91	2	449.45	4.49	.064
ERROR	600.30	6	100.05		
WITHIN SUBJECTS					
24 HRS CONSUMPTION	3675.09	1	3675.09	59.14	.001
LESION X 24 HRS CONSUMPTION	42.32	2	21.16	.34	
ERROR	434.95	7	62.14		

APPENDIX G

MINUTES 55-60 IN THE OPEN FIELD

SOURCE	SS	DF	MS	F	P
BETWEEN SUBJECTS					
LESION	37001.417	2	18500.709	2.639	.099
ERROR	119173.653	17	7010.215		
WITHIN SUBJECTS (REPEATED MEASURES)					
WEEKS	8074.871	4	2018.718	.717	
LESION X WEEKS	7917.092	8	989.636	.351	
ERROR	191465.229	68	2815.665		



Mean number of squares crossed during minutes 55-60 in the open field. Squares are implanted, upward pointing triangles are lesioned only, and downward pointing triangles are controls.

APPENDIX H

LATENCY TO FIRST GRAND MAL SEIZURE

	mean	s.d.	% of animals that seized	ONEWAY ANOVA F
implant	677	607	50%	1.30 (2, 13 df)
lesion only	243	118	100%	
controls	584	478	72%	

(NOTE: a nonparametric Kruskal-Wallas was also nonsignificant)

LATENCY TO THE FIRST ICTAL RESPONSE

	mean	s.d.	ONEWAY ANOVA F
implant	331	258	.54 (2, 13 df)
lesion only	207	77	
control	376	366	

(NOTE: a nonparametric Kruskal-Wallas was also nonsignificant)

SEIZURE DURATION

	mean	s.d.	ONEWAY ANOVA F
implant	50.7	87	0.40 (2, 13 df)
lesion only	227	418	
controls	194	303	

Of the animals that seized, four of the lesioned only, two

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